BRITISH JOURNAL OF OPHTHALMOLOGY

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BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

The vascular factor in low tension glaucoma: alchemists' gold?

The search for evidence of the elusive vascular factor in the pathogenesis of low tension glaucoma continues. In this issue Usui and Iwata report their investigation of alteration in finger blood flow induced by temperature change. They used the same laser-Doppler flow technique as others,[1,2] but have not confirmed the reduced blood flow characteristics identified in these two papers. What are we to make of it? The differences may reflect the different racial characteristics of the subjects in the various studies but much other work on low tension glaucoma produces conflicting evidence, and it is more likely we are trying to produce results with investigative tools which are too crude for the job. Even the definition of low tension glaucoma (or normal pressure glaucoma) is imprecise. It usually depends on the absence of a raised intraocular pressure and the exclusion of other causes of optic nerve or retinal disease. This negative description cannot be satisfactory. Was there raised pressure in the past or are there continuing undetected fluctuations?[3] The difficulty of definition applies equally to primary open angle glaucoma with raised pressure the prevalence of which may vary from 0·4% to 11·2% depending on the diagnostic criteria.[4]

Tests other than finger blood flow have been used in the attempt to identify a systemic vascular abnormality specific to low tension glaucoma. Study of blood coagulation and rheology has proved fruitless.[5] The same authors however claim that multivariate analysis of finger blood flow and haematological factors can distinguish separate groups in both low pressure and high pressure glaucoma.[6] Those patients in whom highest intraocular pressure correlated with severity of field loss had vasospastic finger blood flow measurements and those with no correlation between highest pressure and field loss had disturbed coagulation and biochemical factors. This study depended on impenetrable statistical analysis and even if mathematically sound its biological and clinical significance remains doubtful as the authors themselves point out. The postulated association of low tension glaucoma with carotid stenosis has not been confirmed.[7] An association between migraine and low tension glaucoma has been found by some workers[8] but not by others.[9] Low blood pressure has been identified as a risk factor for progressive visual field loss in elderly glaucoma patients[10,11] and in low tension glaucoma.[10] Yet others find the opposite with higher levels of blood pressure carrying the risk.[12]

Attempts to measure optic nerve blood flow have fared no better yielding only unsatisfactory and contradictory results.[13] However the optic nerve head in low tension glaucoma may be more vulnerable to damage at a lower level of intraocular pressure. There is some evidence to support this view[14] but further studies are required. More convincing support for the concept of low tension glaucoma as a distinct entity comes from visual function studies which suggest that the pattern of field defect varies from high pressure[15-17] glaucoma. Differences in colour vision loss have also been described.[18]

The theory that low tension glaucoma has a specific vascular aetiology remains unproved but there seems to be something in it. We must not let this concept divert attention from the overwhelming evidence now available that raised intraocular pressure, overt, concealed, constant, or intermittent is the greatest risk factor for field loss in primary open angle glaucoma.

J L JAY

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ORIGINAL ARTICLES

Finger blood flow in patients with low tension glaucoma and primary open-angle glaucoma

T Usui, K Iwata

Abstract

Finger blood flow was studied by means of laser Doppler flowmetry in 12 patients with low tension glaucoma (LTG), 12 patients with primary open-angle glaucoma (POAG) and 12 normal subjects. Baseline flow, flow after immersion of the hand in warm water (+40°C), and flow after exposure of the hand in cold water (+4°C) were measured. Statistically significant differences were not found in each flow between the three groups of the patients ($p>0\cdot05$). Vasospastic response to warm and cold water was observed in 25% of LTG patients, 17% of POAG patients, and 25% of normal subjects. There was no significant difference between LTG, POAG, and normal subjects in finger blood flow.

The pathogenesis of optic nerve damage in low tension glaucoma (LTG) and in primary open angle glaucoma (POAG) is still unknown. Recently[1–4] some investigators reported a relationship between LTG and vasospasm. Drance *et al*[5] measured blood flow in the finger in LTG patients with/without migraine and normal subjects with/without migraine. They noted that the mean baseline flow and mean flow after exposure to cold water (+4°C) were lower in patients with LTG, and suggested that vasospastic events might play a role in the damage of the optic nerve head in LTG patients. Corbett *et al*[1] and Phelps and Corbett[2] reported that migraine was frequent in LTG patients; however, our study on the prevalence of migraine in LTG and POAG[6] revealed no significant relationship between migraine and LTG or POAG. Therefore we attempted to investigate further the relation between vasospasm and LTG or POAG, measuring finger blood flow and its response to warmth and cold.

Patients and methods

The patients with LTG had typical glaucomatous optic disc cupping and visual field defects in at least one eye, and intraocular pressure (IOP) without therapy remained lower than 21 mm Hg on repeated measurements; they had no history of retrobulbar neuritis, anterior ischaemic optic neuropathy, or intracranial lesion. The patients with POAG had typical glaucomatous optic disc cupping and visual field defects, and pretreatment IOP of 21 mm Hg or more. Tested normal subjects had no history of vasospastic diseases, such as migraine or Raynaud's disease, and no abnormal ocular findings except refractive error in both eyes. Informed consent was obtained from each subject after explanation of the purpose of the study.

All subjects were seated and adapted themselves in a quiet air-conditioned room. The tests lasted about 10 minutes during which the subjects were not allowed to talk or move.

The laser Doppler flowmeter used in this study, ALF21 (Advance Co, Japan) had a low power (2 mW) semiconductor laser source, producing light at 780 nm wavelength. The volume sampled by the probe was about 1 mm^3. The laser light was delivered to the skin via a flexible optical fibre. The back scattered light consisted of Doppler-shifted light reflected from moving red blood cells and unshifted light reflected from stationary tissue. The back scattered light, both Doppler-shifted and unshifted, was led by another optical fibre from the tissue surface to a photodetector. The signal was processed and amplified to reach a high signal-to-noise ratio, analysed, and was displayed in real time. Values of tissue blood flow were expressed in ml blood/minute/100 g tissue. The output signal from the flowmeter was recorded on paper with pen-recorder (U-228, Advance Co, Japan).

After the probe of the laser Doppler flowmeter was attached to the skin of the middle finger in the subject's right hand by double adhesive tape, the hand was covered with a thin (0·04 mm) glove made of polyethylene. A baseline flow was decided when a steady baseline reading was achieved. The right hand was then immersed in warm water (+40°C) for 2 minutes, and the flow was monitored until a maximum flow was reached after immersion in warm water. The right hand was then placed in ice cold water (+4°C) for 10 seconds, and the flow was monitored for the next several minutes. After immersion in the water the hand was wiped mildly over the glove in order to avoid the influence of heat of evaporation. Blood pressure was also recorded during the test. Student's *t* test was used for the statistical analysis, and the statistically significant level was taken as $p<0\cdot05$.

Results

This study was completed by a total of 36 subjects, including 12 patients with LTG, 12

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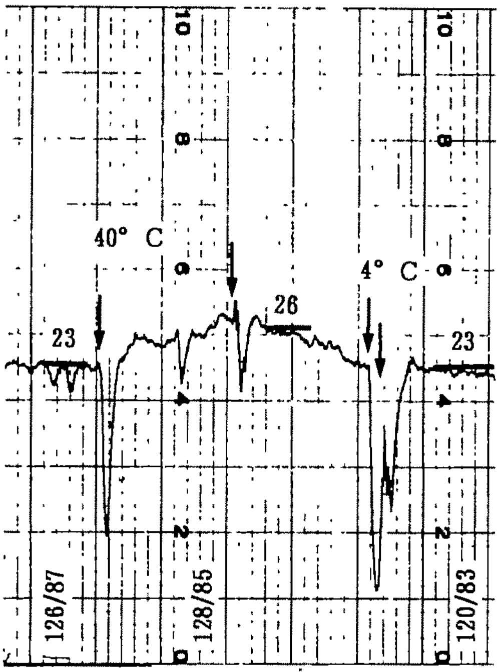

Figure 1 Tracing of finger blood flow in a POAG patient. Normal response to warm and cold water was noted. Values of blood pressure were expressed as mm Hg.

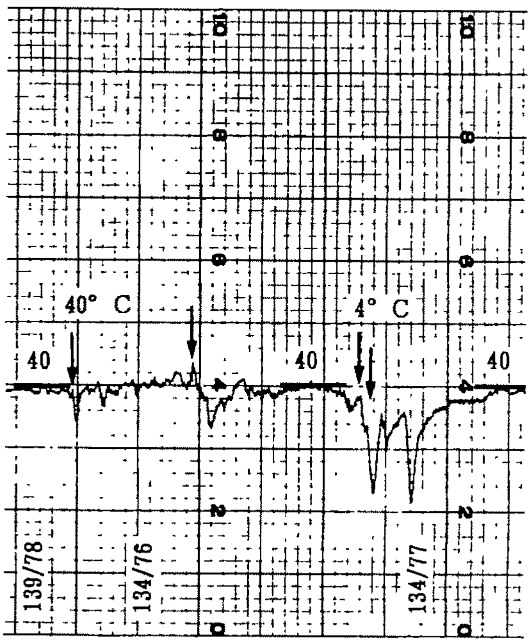

Figure 2 Tracing of finger blood flow in a LTG patient. Normal response to warm and cold water was noted. Values of blood pressure were expressed as mm Hg.

patients with POAG, and 12 normal subjects. The mean age was 47·7 years (SD 8·6) (range 32–61 years) in LTG, 51·7 years (SD 11·5) (range 36–68 years) in POAG, and 44·0 (SD 11·6) years (range 31–63 years) in normal subjects. The mean age of each of the three groups showed statistically no significant difference (p>0·05). The mean untreated IOP was 14·6 mm Hg (SD 2·9) in LTG, 27·9 mm Hg (SD 4·8) in POAG, and 15·2 mm Hg (SD 3·2) in normal subjects.

The patients in Figs 1 and 2 showed normal response to warm and cold water. They showed little increase in flow after exposure to the warm water and a decrease in flow during and after a short exposure to cold water, but the flow quickly returned to baseline. Figs 3 and 4 gave the vasospastic response according to Drance *et al.*[5] The patients had marked response to warm and cold water, but without recovery to baseline flow. Three of 12 LTG patients, two of 12 POAG patients, and three of 12 normal subjects showed this response.

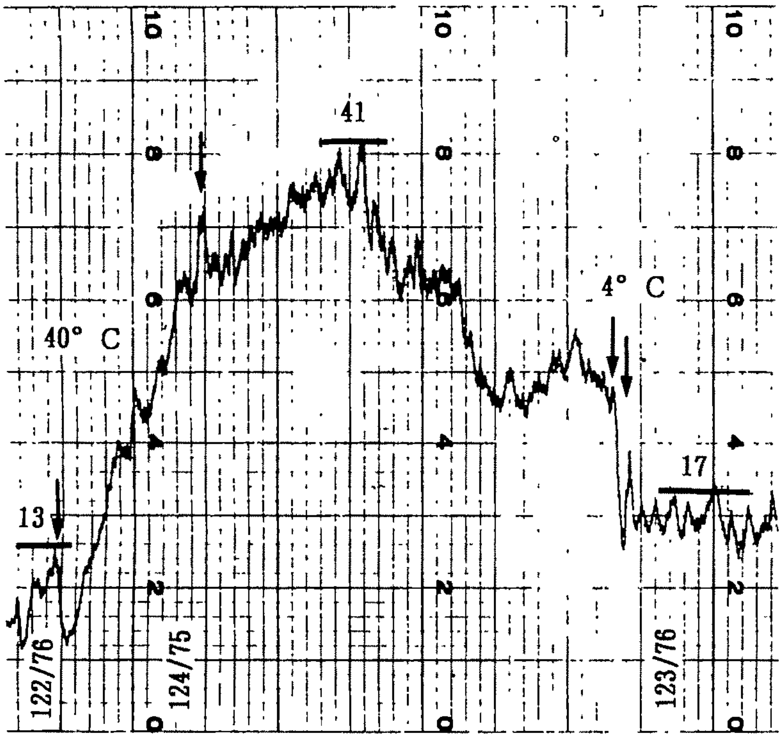

Figure 3 Tracing of finger blood flow in a normal subject. Vasospastic response was demonstrated. The flow had marked response to warm and cold water, but without recovery to baseline flow. Values of blood pressure were expressed as mm Hg.

Finger blood flows in LTG, POAG, and normal subjects are summarised in Table 1. Baseline flow, flow after heat, and flow after cold in LTG patients were somewhat lower than those in POAG patients or normal subjects. However, no statistically significant difference was found in the three groups (p>0·05). Furthermore, we calculated flow after heat/baseline flow, flow after cold/baseline flow, and flow after heat/flow after cold. Again there was no statistically significant difference in the three groups (p>0·05).

Discussion

Laser Doppler flowmetry (LDF) is a clinically useful method of measuring local blood flow non-invasively and continuously.[7-12] Usually LDF is applied to studies of skin blood flow, because it gives a continuous signal and is applicable to any region, and the measuring depth is limited to cutaneous tissue.[13 14]

Blood flow through cutaneous arteriovenous anastomoses is controlled by specific thermoregulatory reflexes, whereas capillary blood flow is the target of local temperature effects.[15 16]

Drance *et al*,[5] applying LDF, reported that the mean baseline flow and mean flow after exposure to cold water were lower in LTG patients. However, in our series a statistical significant difference was not found (p>0·05). They found that 65% of the LTG patients without migraine

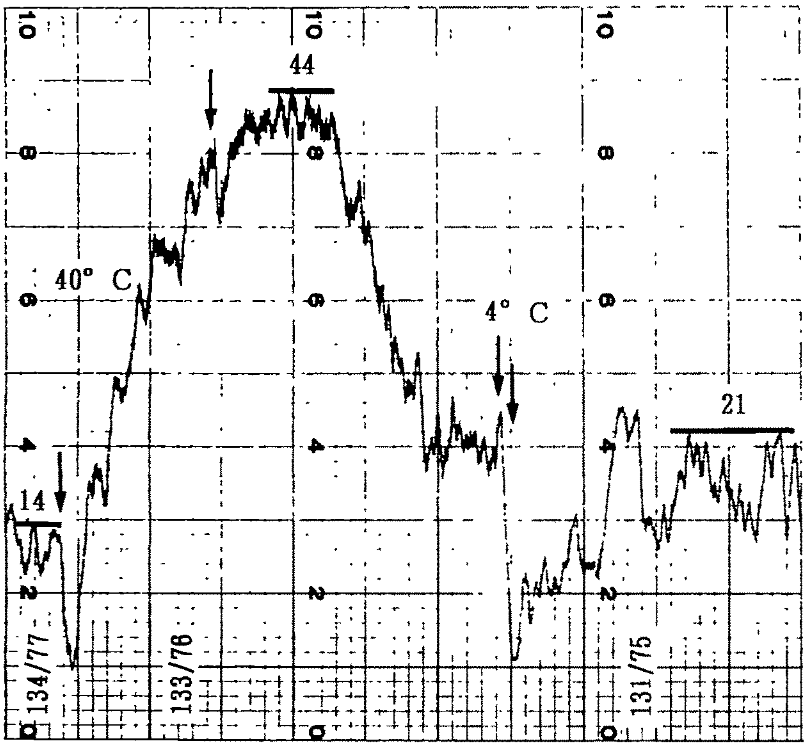

Figure 4 Tracing of finger blood flow in a POAG patient. Vasospastic response was demonstrated. Values of blood pressure were expressed as mm Hg.

showed vasospastic response, but in our series only 25% of the LTG patients, 17% of the POAG patients, and 25% of the normal subjects showed such a response. In our study the frequency of vasospastic response in normal subjects was almost the same as in the normal subjects in Drance's report (26%). Patients who showed vasospastic response in our study had no history of vasospastic disease, such as migraine or Raynaud's disease. 'The vasospastic response' which Drance *et al* designated in their study might not reflect the vasospastic disease.

The pathogenesis of optic nerve damage in POAG is not clear and ischaemic theory has been supported by many ophthalmologists. This theory proposes that elevated IOP produces relative ischaemia of the optic nerve head and damages axons. Therefore the presence or absence of vasospastic response in POAG is an important problem to be solved. In our series there was no statistically significant difference in vasospastic response between POAG patients and normal subjects.

Table 1 Mean finger blood flow (with SD) in patients with LTG, POAG, and in normal subjects

	LTG (n=12)	*POAG (n=12)*	*Normal (n=12)*
Age	47·7 (8·6)	51·7 (11 5)	44·0 (11 6)
Baseline flow	26·2 (9·8)	28·0 (10 8)	31·0 (8 7)
Flow after heat	34·0 (10·4)	35·8 (10 4)	38·9 (8 0)
Flow after cold	26·3 (9 4)	30·3 (11·6)	32 6 (7 7)
Flow after heat/ baseline flow	1·42 (0 49)	1·41 (0·60)	1 35 (0 57)
Flow after cold/ baseline flow	1 01 (0 12)	1·11 (0 17)	1·08 (0·13)
Flow after heat/ flow after cold	1·45 (0·67)	1·26 (0·36)	1·23 (0 36)

*The finger blood flows are expressed as ml blood/minute/100 g tissue.

Several investigators reported that the vasospastic process caused visual disturbances.[17 20] Lewis *et al*[20] indicated that 35% of migraine patients had some form of visual field abnormality, such as left homonymous deficit, generalised depression, arcuate defect, altitudinal defect, temporal sector, nasal steps, and isolated scotomas. Thus ischaemia was generally presumed to be the main cause of the optic nerve damage in LTG and POAG as well. However, it should be noted that, even though there is clinical similarity between ischaemic damage and glaucomatous damage in the optic nerve, the pathogenesis is not always the same. The pathohistology of the optic nerve head has revealed a different pathogenesis.[21] Our study also failed to confirm the relationship between vasospasm and LTG or POAG.

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Controlled trial of laser photocoagulation of pigment epithelial detachments in the elderly: 4 year review

M J Barondes*, S Pagliarini†, I H Chisholm, A M Hamilton, A C Bird

Abstract

Patients who were enrolled in a controlled treatment trial of laser grid photocoagulation for retinal pigment epithelial detachment as part of age-related maculopathy were reviewed 4 years after entry into the trial. The data imply that the original conclusion that this form of treatment did not improve the visual prognosis at 18 months was also justified at 4 years. It has become clear that lesions with evidence of subpigment epithelial new vessels were included in the trial. In a retrospective study the lesions were separated into those in which there was evidence of subretinal neovascularisation and those in which no such evidence existed. A difference was identified in the behaviour of the treated and untreated lesions designated avascular in that the treated eyes had a poorer visual outcome. These cases accounted for the different behaviour between two management groups in the initial study such that the original conclusion that grid photocoagulation of avascular pigment epithelial detachments in the elderly does not improve the visual prognosis is justified.

The initial reports on treatment of retinal pigment epithelial detachments (PEDs) by photocoagulation appeared to imply therapeutic benefit to the patients. The technique involved photocoagulation of the temporal periphery of the lesion with light from a xenon arc[1] or laser.[2] Subsequently a grid of applications over the surface of the lesion was adopted as the preferred management.[3] The mechanism by which the PED was caused to flatten was unknown although subsequent evidence implies that reducing the fluid pumped by the pigment epithelium towards the choroid from retina or disruption of the deposits on the inner surface of Bruch's membrane may have contributed to the observed effect.

Although these early studies were encouraging it is evident that many patients treated were young and did not have the poor untreated prognosis of age-related macular disease.[4,5] For this reason a randomised treatment trial of avascular PED was undertaken in patients older than 50 years who also had other signs of age-related maculopathy. A grid pattern of argon laser photocoagulation was used. Recruitment was terminated after 18 months when early results showed greater visual loss in treated eyes than in untreated controls.[6] The validity of this study as it pertains to 'avascular' lesions is in doubt since many of the patients recruited to the study had indirect evidence of subpigment epithelial new vessels.

The patients have now been reviewed over a 4 year period so that the long term behaviour of the treated and untreated groups can be compared. The entry angiograms have been reassessed as to the presence or absence of new vessels using revised criteria[7] to identify whether or not the conclusion concerning the benefits of photocoagulation is justified.

Materials and methods

The entry fluorescein angiograms and subsequent records of patients enrolled in the Moorfields treatment trial of PEDs was reviewed. After suspension of the trial patients were asked to return at 2 years and then yearly. Visual acuity, morphological appearance, fundus photographs, and fluorescein angiograms were assessed at each visit. Visual acuity was always measured in the same room with best correction by a worker who was masked from the form of management.

Forty nine eyes were included in the original treatment trial. Two patients who died before the 6 month visit and one who was lost to follow up before the 18 month visit were excluded from the review. Another four photographic files could not be located, leaving 42 eyes in 42 patients available for review. Of these 20 had been treated and 22 were controls. Visual and morphological outcomes were reviewed.

The lesions were reclassified as to the likely presence or absence of subpigment epithelial new vessels. The following criteria were used to indicate their presence: haemorrhage, exudate, irregular fluorescence not explained by irregular pigmentation of the detached tissues, early and pronounced hyperfluorescence at the edge of the lesion, a notch, and hyperfluorescence beyond the edge of a lesion at the site of a notch.[2] The behaviour of the treated and untreated lesions was compared in the two groups using Student's *t* test.

Results

VISUAL ACUITY

The review study attendances of the treated (n=20) and untreated (n=22) patients were similar. Of the 20 treated patients 18 attended the 18 month visit as did 21 of the 22 observed patients (Table 1). At the 4 year visit 15 of the 20 (75%) treated patients and 19 of 22 (86%) untreated patients were seen. Data beyond 4 years was not considered since half of the patients did not return for their 5 and 6 year visits.

In the treated eyes visual acuity loss occurred early with a mean loss of 2·16 lines at the 3 month visit. This loss remained stable during the first 18 months of review and slowly declined thereafter.

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Control eyes showed gradual but progressive visual loss throughout the period of review (Table 1). The difference between the two groups narrowed with time; a difference was still present at 2 years but was not seen at 4 years.

Visual acuity less than 6/24 was more common in treated eyes than in control eyes at 3 months and 2 years but by 4 years the numbers were similar in the two groups (Table 2).

MORPHOLOGICAL OUTCOME

Geographic atrophy was more common and occurred earlier in the treated eyes whereas the numbers with subretinal new vessels and tears of the retinal pigment epithelium in the two groups were similar (Table 3). In the treated eyes tears appeared soon after therapy whereas in the control eyes they occurred at some time during the first year after recruitment to the trial. Persistent detachment of the retinal pigment epithelium was seen only in those patients who were untreated. These eyes had a favourable course losing only 1·00 line of acuity at the time of the last review whether or not there was indirect evidence of subpigment epithelial new vessels. This is in contrast to those with new vessels clearly seen in the subretinal space and atrophy or tears of the RPE which gave poor vision.

Table 1 Attendance and visual loss in treated and untreated eyes

	Treated		Untreated			
Visit	No	Lines lost	No.	Lines lost	t	p
Initial	20	–	22	–		
3 month	19	2 16	20	0·30	2823	0·008
6 month	18	2 50	22	0·68	2857	0·0079
9 month	16	2·50	18	0 72	2622	0·013
1 year	18	2·44	20	0·95	2199	0·034
1·5 year	18	2 66	21	1·13	1959	0·058
2 year	19	3·21	19	1·79	1699	0·098
3 year	15	2 93	19	2·42	0·697	0·491
4 year	15	3 33	19	3·37	−0 0444	0·965

t=Student's *t* test, *p*=provability of error.

Table 2 The number of eyes with vision worse than 6/24 in treated and untreated eyes

	Treated eyes		Untreated eyes	
Visit	Patients	VA <6/24	Patients	VA <6/24
3 months	19	7 (36%)	20	2 (10%)
2 years	19	11 (57%)	19	7 (36%)
4 years	15	10 (66%)	19	14 (73%)

VA=visual acuity.

Table 3 Visual acuity (VA) in Snellen's lines loss compared with morphological outcome

	Treated			Untreated		
Outcome	No. (%)	Onset*	VA loss	No (%)	Onset*	VA loss
Geographic atrophy	10 (50)	1	2·6	5 (23)	3·8	2·6
SRN	8 (40)	2·3	4·9	10 (50)	2·2	4·3
Persistent PED	0	–	–	5 (23)	4 0	1·0
RPE tear	2 (10)	0·25	5·0	2 (9)	0·5	5 0

*=Onset in years after entry into trial. SRN=subretinal neovascularisation. PED=pigment epithelial detachment. RPE=retinal pigment epithelium.

Table 4 Snellen's lines visual acuity loss in those patients in whom categorisation as vascular and avascular was unanimous

	Vascular PEDs		Avascular PEDs	
Review (years)	Treated	Control	Treated	Control
0·25	−2·20	−0 50†	−4·83	−0·17*
0·50	−2·75	−1·75	−4·50	−0 29*
0·75	−3·00	−2·67	−4 40	−0 50*
1·00	−3·00	−3·75	−4·67	−0·33*
1·50	−3·40	−4·00	−4·50	−0·29*
2·00	−4·60	−4·66	−4·33	−0 20†
3 00	−4·75	−4·66	−3·60	−0 33†
4 00	−4·75	−5·60	−3·80	−1·17‡

*p<0·001; †p<0·01; ‡p=0 01.

CORRELATION WITH INITIAL CLASSIFICATION

There were 10 lesions which were classified as vascular by all three readers.[7] Of these six received grid photocoagulation. The two groups behaved in a similar fashion after therapy although acuity was lost slightly more quickly in those who were treated (Table 4). The major loss of acuity was within the first 3 months in these patients whereas in the controls the loss occurred over the first year.

Thirteen lesions were designated as avascular; six were treated and seven untreated. In the treated group major visual loss occurred in the initial 3 months after photocoagulation. This was due to tears of the pigment epithelium or to atrophy which accompanied flattening. By contrast the controls had little loss of acuity until the fourth year. Despite the small numbers the deficit in the treated patients was significantly greater than in the controls up to 3 years after entry into the trial.

Discussion

The controlled trial showed that there is substantial risk of early visual loss in treated eyes by 18 months. A 2 line reduction in Snellen acuity was recorded in 73% of eyes randomised to treatment and 41% of untreated eyes. The early results from this study discouraged many ophthalmologists from treating avascular PEDs.

After 4 years of review convergence of visual acuity in the two groups is attributable to gradual worsening of vision of the untreated eyes rather than to delayed improvement in the treated eyes. The equilibration of visual loss might be expected considering the natural history of untreated PEDs in the elderly. The extent of visual loss in the untreated eyes is similar to that reported previously.[8–13] Treatment apparently hastened the visual loss that would otherwise occur at a slower pace.

The morphological outcome of treatment and control eyes differed. Persistent detachment occurred exclusively in untreated eyes; the retention of good visual acuity (one line of acuity lost) in these eyes has been reported.[11] Tears of the pigment epithelium may complicate treated or untreated PEDs[14] and did occur with similar frequency in treated and untreated eyes. It appears that treatment precipitates a tear in a lesion which is predisposed to such a complication rather than causes an event which would not otherwise have occurred. The incidence of subretinal neovascularisation in both groups was similar and is within the range of 24 to 67% cited by others.[8–13, 15, 16] It is also implied that subpigment epithelial neovascularisation is not an inevitable association or consequence of PEDs. The incidence of atrophy was higher in treated eyes (50%) than in the control eyes (23%) and was associated with visual loss. Atrophy occurred soon after treatment in the treated eyes while the onset in control eyes was delayed until the third or fourth year when it followed spontaneous flattening of the detachment. Evidence suggests that metabolic failure of the RPE may be responsible for resolution of the detachment and the ensuing geographic atrophy.[13, 17, 18] Destruction of the RPE by laser photocoagulation might hasten or exaggerate this process.

The objective of the original controlled trial was to test the benefits of grid laser treatment on avascular PEDs but the analysis indicates that a heterogeneous group of patients was recruited into the study.[7] This review showed that many entry angiograms showed signs believed to imply the presence of new vessels and it was in these lesions that new vessels appeared. On extended follow up 55% of the patients developed subretinal neovascularisation. Although the numbers in which all three observers agreed on reclassification of lesions are small there is no indication to modify the original conclusion that grid laser photocoagulation, as undertaken in the original trial, does not improve the visual prognosis in 'avascular' retinal pigment epithelial detachments as a manifestation of age-related maculopathy. The major difference in behaviour of the treated and control groups as previously reported[6] was early loss of visual acuity in the former. It appears that those lesions redesignated as avascular accounted exclusively for this difference in response. A treatment method which flattens detachments while producing minimal tissue damage might preserve vision more effectively. This does not prove that other techniques of photocoagulation would not be successful[20] but emphasises the desirability of a different approach to therapy.

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Detection of subpigment epithelial neovascularisation in cases of retinal pigment epithelial detachments: a review of the Moorfields treatment trial

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Abstract

The entry angiograms of 42 eyes with detachment of the retinal pigment epithelium in a treatment trial of laser photocoagulation were reviewed in a masked fashion by three observers in order to assess the possible presence of subpigment epithelial neovascularisation. Vascularity or avascularity was designated with reference to a list of clues believed to imply the presence of subpigment epithelial neovascularisation. As a predictor of outcome the initial assessment achieved a sensitivity and specificity of 77% and 82% respectively. Despite notable parity of the degree of sensitivity and specificity among the three observers, full agreement on the initial assessments was reached in only 23 eyes (55%), 10 with vascular and 13 with avascular outcome. Of these, only one eye which developed new vessels after 4 years had an outcome which differed from that predicted by classification of the entry angiograms.

Retinal pigment epithelial detachment (PED) as a consequence of age-related maculopathy represents an important cause of irreversible visual loss in the elderly.[1-4] Some PEDs occur without demonstrable neovascularisation in the subpigment epithelial space while in others fluorescein angiography shows new vessels or there is indirect evidence of their presence.[2-8] Histological studies imply that new vessels from the choroid may have already invaded the space between the detached pigment epithelium and Bruch's membrane even when angiography has failed to demonstrate their presence.[9,10] Uncertainty as to the presence and extent of subpigment epithelial blood vessels accounts, in part, for differences in the reported natural history of PEDs[4,5,7,8,11-22] and for their unpredictable response to treatment.[8,11,16,23-28] It has now become apparent that if blood vessels are not clearly shown by fluorescein angiography certain characteristics of the lesion such as irregular punctate hyperfluorescence,[3,5,7,18,29] flattening or indentation of the smooth convex border (notches),[5,20,29] hyperfluorescence beyond the edge of the lesion at the site of a notch,[5,7,30] and early pronounced hyperfluorescence at the edge of the PED may imply their presence.

A treatment trial of laser photocoagulation for this disorder was suspended after 18 months when results showed an excess of visual loss in treated eyes when compared with controls.[26] Entry criteria had excluded patients with clear evidence of choroidal neovascularisation such as haemorrhage, exudate, regional masking not related to hyperpigmentation, progressive subpigment epithelial hyperfluorescence (hot spots) and a manifest leaking subretinal capillary complex. Because of the more recently described indicators of neovascularisation, there is considerable doubt as to the validity of the conclusions drawn from the original therapeutic study as it may apply to 'avascular' PEDs. This has prompted us to review the original angiograms, and to reclassify them in the light of the changing criteria for the detection of new vessels and to compare the revised designation with the subsequent outcome of disease. The influence of the reclassification upon the conclusions as to therapy are described elsewhere.[31]

Materials and methods

We reviewed the entry fluorescein angiograms from the treatment trial[24] for signs of subpigment epithelial neovascularisation. The treatment trial included 49 PEDs within 1500 μm of the foveal centre in patients aged 50–80 years. Of these all but four involved the centre of the fovea. The trial had excluded eyes with clear evidence of subretinal new vessels using the following criteria: the presence of visible new vessels on angiography, haemorrhages, and exudates. Eyes randomly assigned to laser treatment had treatment repeated at 2 week intervals up to three times until the detachment flattened or new vessels were detected. Follow up visits were scheduled every 3 months during the first year of the trial and again at 18 months. After suspension of the trial patients were asked to return at 2 years, and yearly thereafter. Visual acuity, morphological appearance, fundus photographs, and fluorescein angiograms were assessed at each visit.

Of the 49 patients recruited into the treatment trial, we excluded from our review two who died before the 6 month visit and one who was lost to follow up before the 18 month visit. Another four photographic files could not be located. The entry angiograms of 42 eyes in 42 patients remained for assessment.

The entry stereoangiograms were reviewed by three observers who were masked from the final outcome and from each other's assessments. Entry angiograms were evaluated for the presence or absence of subpigment epithelial neovascularisation; every effort was made to designate a lesion to either category although some lesions proved unclassifiable. Subpigment epithelial neovascularisation was considered to be present if the following features were found: haemorrhage, exudate, irregular fluorescence, early and pronounced hyperfluorescence at the edge of the lesion, a notch, and irregular hyperfluorescence beyond the edge of a lesion which was usually at the site of a notch.

The predictive value of each observer's assessments was determined by comparing the original classification with the morphological outcome during review. The development of new vessels during the period of review was shown by the presence of subretinal haemorrhage, exudates, or frank subretinal neovascularisation (fibrovascular disciform scar or leaking subretinal capillary plexus). A PED which showed no evidence of neovascularisation, whether it flattened spontaneously with or without atrophy, ripped, stayed unchanged, or developed geographic atrophy, was considered to have an avascular outcome.

Because the correlation of the initial classification and subsequent outcome was the same whether or not the lesion was treated the results have been analysed as a single population.

Results

Data were available on 42 patients up to 18 months, 38 patients to 2 years, and 34 patients to 4 years. Of the eight patients who missed the 4 year visit four had vascular outcomes manifested by haemorrhagic disciform lesions at an earlier visit. Of the remaining four patients, two remained avascular at 1·5 years and two at 2 years.

The specificity for correct prediction of vascular or avascular outcome was 78%, 80%, and 89% and the sensitivity 74%, 79%, and 79% for observers 1, 2, and 3 respectively (Table 1). No classification was given by the three observers in 3%, 5%, and 12% of cases.

Full agreement was reached in only 23 eyes (55%), 10 of which were classified as vascular and 13 as avascular; both groups contained treated and untreated patients. All 10 eyes identified by each observer as 'vascular' subsequently developed undoubted evidence of subretinal neovascularisation. Of the 13 eyes designated as avascular by all three observers only one developed subretinal neovascularisation and this occurred after the 4 year visit.

Discussion

The correlation between the designation of the lesion at entry to trial and the subsequent outcome of PEDs using ophthalmoscopic and angiographic clues supports the validity of the criteria used in this study to indicate the presence of subpigment epithelial new vessels. There was close but not perfect parity between the three observers for specificity and sensitivity. Particularly noteworthy was the good correlation between those classified as vascular and the subsequent behaviour of the lesion. However from the lack of agreement between observers it is evident that the interpretation of clinical signs is imprecise. Of the criteria used the significance of uneven filling and marginal hyperfluorescence were the most difficult to assess, while the presence of notches was relatively easy to recognise. This inconsistency might be avoided with the use of standardised photographs which define each clue although the interpretation of fluorescein angiograms is imprecise. For instance irregular hyperfluorescence within a PED or in the adjacent retina may signal the presence of occult new vessels but may also be due to uneven binding of dye in Bruch's membrane and detached tissues or to irregular blockage of fluorescence by pigment in the detached pigment epithelium. The pigment may be blood or melanin which can be seen ophthalmoscopically or lipofuscin which cannot be detected. It was lesions with uneven filling that accounted for most disagreement between the three observers and for the undesignated cases. The best specificity scores were achieved by the observer with the largest number of cases which were unclassified.

Table 1 Comparison of classification and subsequent outcome of lesion

	Entry assessment (n=42)			*Specificity*			*Sensitivity*		
	Vasc	*Avasc*	*?*	*Vasc*	*Avasc*	*Overall*	*Vasc*	*Avasc*	*Overall*
1	16	24	2	14/16	17/24	31/40 (78%)	14/23	17/19	31/42 (74%)
2	19	22	1	16/19	17/22	33/41 (80%)	16/23	17/19	33/42 (79%)
3	22	15	5	19/22	14/15	33/37 (89%)	19/23	14/19	33/42 (79%)

Vasc=vascular PEDs.
Avasc=avascular PEDs.
?=cases in which no definite prediction could be made.

More encouraging is the fact that only one case of the 23 with unanimous designation behaved in a way different from that predicted whether or not the lesion was treated. The single exception did not have undoubted evidence of neovascularisation until more than 4 years of review. This indicates that the clinical clues are valid predictors of subsequent behaviour of the lesion. These data also imply that whatever effect photocoagulation had upon the lesion, it did not seem to influence the incidence of detectable neovascularisation.

It is surprising that the ability to predict the long term outcome was so good albeit in only a few cases. It appears that a lesion which has no features of new vessels is unlikely to develop detectable new vessels during the evolution of the lesion. The designation of a lesion as avascular during the period of assessment does not prove that new vessels did not exist in the subretinal space at any time since there is evidence they may resolve spontaneously[32] or remain unseen. If cases existed with subpigment epithelial new vessels which were not indicated by angiography the blood vessels did not appear to alter the course of the disorder.

These observations show that vascular or avascular evolution of PEDs could be predicted with some accuracy using the clinical signs believed to imply the presence of subpigment epithelial new vessels. Agreement among the three observers further reduced the probability of error. Since the prognosis and possible new therapeutic approaches may differ for vascular and avascular PEDs the ability to detect new vessels reliably might promote the development of more effective therapeutic methods.

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A primate model for age related macular drusen

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Abstract

A closed colony of semi-free-ranging rhesus monkeys maintained in isolation since 1938 by the Caribbean Primate Research Center (CPRC) is being studied as a model for age related macular drusen. Of examined colony animals 57·7% of the monkeys and 47·3% of their eyes have drusen. The prevalence and severity of drusen are linearly related to increasing age and are significantly higher in specific maternal lineages (matrilines). An electrophysiological estimate indicates loss of function associated with drusen. Prevalence of drusen in CPRC females is almost twice that of males, while the prevalence among CPRC animals in general appears to be several times that of monkeys from continental US facilities. Evidence suggests that the frequency of end-stage lesions is also similar to that in human populations. The CPRC matriline monkeys appear to provide the best model yet reported for human age related macular drusen.

Age related macular degeneration (AMD) is a major cause of severe vision loss in the United States and the major cause in persons over 50.[1,2] The initial clinical manifestation of AMD,[3] and one of the most important,[4] is drusen. These are visible ophthalmoscopically as yellow-white spots in the retinal pigment epithelium (RPE) and are seen histologically as depositions of pleomorphic material beneath the RPE.[3-6] Given the significance of drusen in AMD and failure to induce them in normal eyes, it would be valuable to identify an animal species in which drusen occur spontaneously. There have been several reports of drusen and macular lesions in aging monkeys,[6-15] but the condition appears rare in animals in US facilities. We have been investigating the incidence of macular signs associated with this disease in a closed colony of free-ranging rhesus macaques (*Macaca mulatta*) at the Caribbean Primate Research Center (CPRC) of the University of Puerto Rico. While samples from this population have been described,[6-11] we report new relationships between drusen and aging, resolution loss, sex, and colony matriarchal lineages.

Material and methods

The colony was established on Cayo Santiago, a small island off the east coast of Puerto Rico, in 1938 and no new animals have been introduced since.[16] Since 1956 all monkeys have been individually identified and daily census records maintained. The social history and matriarchal lineages (matrilines) for eight to 10 generations are known for each animal. Commercial monkey diet and water are provided in addition to natural forage. Only social and behavioural observations are allowed on the island except during annual medical examinations, when limited, non-invasive, biomedical research is possible. Animals removed to reduce the colony's size are housed, with a number of non-colony animals, in large, outdoor corrals at a second facility (Sabana Seca) on the Puerto Rican mainland. The CPRC maintains over 2000 monkeys, the majority being derived from original Cayo Santiago matriarchs.

We conducted 315 eye examinations on 246 monkeys from the Cayo Santiago matrilines. Sixty-one of these were repeat examinations after one to three years, and eight were accidental duplicates (after one to two days). Examinations were conducted at Sabana Seca and on Cayo Santiago. Only data from animals with traceable Cayo Santiago lineages are included in this report.

All monkeys were anaesthetised by initial intramuscular injection of ketamine hydrochloride (12 mg/kg, Vetalar), with supplementation (6–12 mg/kg) as necessary to maintain an effective level of anaesthesia. Pupils were dilated with phenylephrine (10%, Neo-Synephrine) and tropicamide (1%, Mydriacil). Corneas were kept moist with artificial tears (Tears Naturale) and anaesthetised with propacaine (0·5%, Alcaine).

Eye examinations consisted of notation of abnormalities of the externae and anterior segments, intraocular pressure measurement, indirect and direct ophthalmoscopy, and, for some affected monkeys, fundus photography and, rarely, fluorescein angiography. The animals were not refracted but extreme refractive errors were noted when detected under direct ophthalmoscopy.

In the retinal examinations gross abnormalities were noted, cup/disc ratios estimated, and detectable macular drusen were counted, under direct ophthalmoscopy, up to 15. The drusen counts were recorded either directly or in quantitative increments of five, as 0, ≤5 . . . ≤15, >15. The counts were later used to categorise each eye on a five point drusen category scale (0 to 4) based purely on the numbers of drusen, as: 0=0 drusen, 1=≤5 drusen, 2=>5 and ≤10 drusen, 3=>10 and ≤15 drusen, and 4=>15 drusen.

Drusen counts were conducted by two or more of three examiners. Initially, the drusen count for each eye was reached by consensus but more recently was taken as the mean of independently conducted and recorded counts by each of the three examiners. Multiple correlation analysis of these data indicate that the agreement among examiners is very close ($r=0{\cdot}89$) with a standard error of estimate of less than two drusen (1·84). This correlation is statistically significant ($p<0{\cdot}01$). Analysis of variance also indicated that there were no significant differences among the examiners ($F=0{\cdot}50$, $F\,(0{\cdot}75)=1{\cdot}39$, W/2,142 df). Comparisons based on drusen categories yielded kappas[17] between 0·40 and 0·50 for pairs of examiners. These levels of agreement are significantly ($p<0·001$) greater than would be expected by chance. In addition the eight animals (16 eyes) accidentally re-examined on successive days provided a useful estimate of the repeatability of the measures. Drusen categories on the initial and repeat examinations were identical for 14 of the 16 eyes (6 at 0, 6 and 1, and 2 at 4) and differed by only one category unit (3 *v* 4) for two eyes of one animal. The test-retest correlation coefficients were 0·98 for eyes and for animals, both statistically significant ($p<0·01$). The age and parentage of the animals were unknown to the examiners until after completion of the examinations, when these data were determined from the matriarchal lineages.

Fundus photographs and fluorescein angiograms were taken with a Kowa hand-held fundus camera which had been modified to carry a 35 mm camera back (Pentax MX) and autowinder (Pentax). Angiograms were taken with appropriate barrier and exciter filters at 1-second intervals for 20 seconds following fluorescein injection (10 mg/kg, Fluorescite) and after 30 seconds and 3 minutes. Extensive fundus photography was not feasible under the primitive conditions on the island where over half of these animals were examined. All ophthalmic equipment was transported daily by small boat across open water to Cayo Santiago, then by hand up the island's highest hill. Examinations were conducted in an open air shelter with no light control and with unregulated electricity from portable generators. Electricity was shared and consequently was frequently inadequate for fundus camera operation. The adequacy of the photographic records could not be verified until after the opportunity to collect data was lost. Finally, small lesions clearly visible through the direct ophthalmoscope were undetectable through the fundus camera or in photographs. Under these conditions the certainty, instant verification, and greater magnification provided by the direct ophthalmoscope proved much more suitable than fundus photography for determination of quantities of drusen.

Eight monkeys shipped to our laboratories for electrophysiological estimates of visual resolution were anaesthetised and their pupils were dilated (as above). They were maintained on 25% oxygen, 75% nitrous oxide, muscle relaxant (pancuronium bromide, Elkins-Sinn), and intravenous saline. Core temperature, electrocardiogram and end tidal CO_2 were monitored. All procedures were approved by the relevant Institutional Animal Care and Use Committees. Signals in response to counterphased patterns, projected on to the macula under visual control for location and focus via a modified Zeiss fundus camera, were led to specially designed low-noise preamplifiers, then processed and stored by digital computer (Nicolet Med 80). The root mean square (RMS) amplitudes were later determined from the stored signals and provided the basic data for resolution estimates.

Primary dependent variables evaluated in this report were prevalence of drusen, indicated by the percentages of animals and/or eyes in which drusen was present; and the relative severity, indicated by the quantitative drusen category into which each retina fell; and the visual resolution estimate described above. In most cases analyses are presented for affected monkeys and for affected eyes, consistent with similar human studies.[18] Data were evaluated statistically by analysis of variance, *t* tests, regression/correlation, and non-parametric χ^2 analyses for contingency tables.

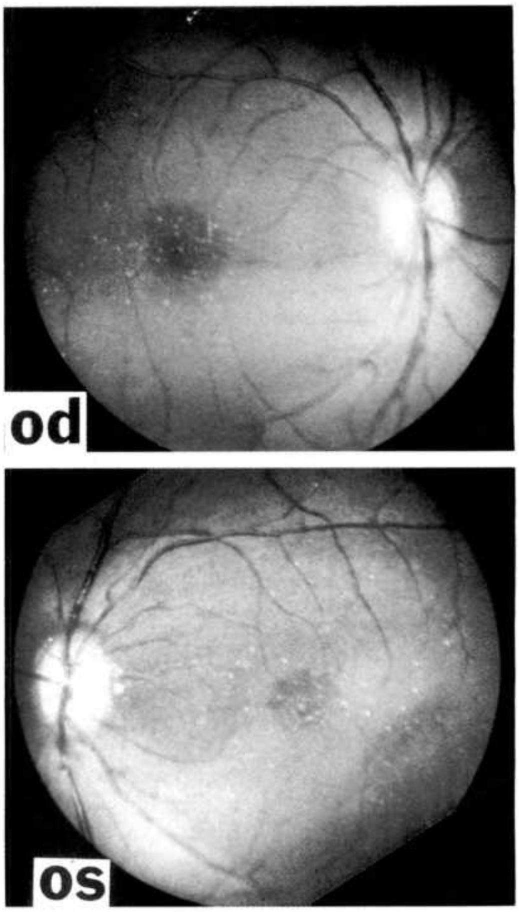

Figure 1 Fundus photographs of typical category 4 retinas. Numerous drusen are obvious in both the right (OD) and left (OS) fundi.

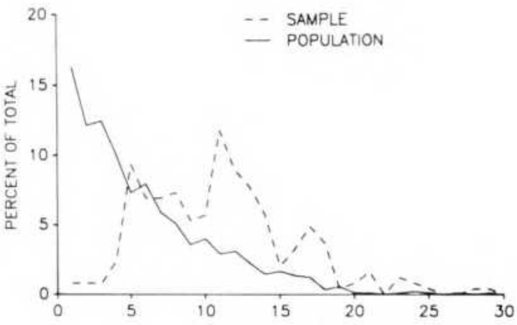

Figure 2 Age distribution of Cayo Santiago macaques. The left ordinate presents the percentages of animals at each year of age indicated on the abscissa. Distributions of the colony (solid line) and our sample (broken line) are presented. The majority of the animals in the sample distribution were over 10 years of age.

Results

Figure 1 presents right and left eyes of monkey no. 909, an 11 YO (at examination) female from matriline 091. Both eyes of this animal fell into drusen category 4 (>15 drusen). The lesions seen here are typical of those seen in the eyes of CPRC monkeys. Note that drusen in OS appear to be larger, confluent and more foveal than in OD.

Age distributions (Fig 2) show that our sample was selective for older animals, while the colony distribution was heavily skewed by large numbers of very young monkeys.[19] The majority of our sample were over 10 years of age. Ordy and Brizzee[20] have estimated that one monkey year is equal to about 3–3.5 human years. By this estimate our sample ranges up to the human equivalent of about 85–100 years of age.

A total of 490 fundi from the 246 animals from the Cayo Santiago matrilines were examined (cataracts obscured two fundi). Drusen were found in 142 of 246 animals (57·7%) and in 232 of the 490 retinas (47·3%). Ages of animals whose retinas contained drusen ranged from 3 to 29 years, or 9–10 to 85–100 human years.[20] Percentages of affected animals and eyes increased linearly with increasing age (Fig 3). The correlations, $r=0{\cdot}858$ and $r=0{\cdot}861$, are significant ($p<0{\cdot}01$) and suggest that 74% of the variability in prevalence can be accounted for by age. Figure 4 shows a similar relationship between mean drusen category and age. The correlation coefficient ($r=0{\cdot}83$, $p<0{\cdot}01$) by this measure indicates that 69% of the variability in drusen category (severity) is accounted for by age in our cross-sectional sample.

Longitudinal evidence indicates progression of the disease in 57 matriline animals re-examined after one to three years. Thirty (52·6%) of these monkeys and 59 of the 114 (51·7%) eyes showed quantitative increases in drusen. The quantity of drusen decreased in 10 eyes of six animals over the same period. Most changes involved less than five drusen, though some monkeys went through several drusen categories. The observed proportions were significantly different ($p<0{\cdot}001$) from those expected under the assumptions of no increase or of random variability.

Of the 246 individual animals comprising the sample 114 were males and 132 were females. In Table 1 females can be seen to be significantly higher than males in every category of drusen prevalence or severity, for animals or eyes. Only differences in ages and numbers of males and females in the sample were not statistically significant. Regression analyses for prevalence among males and females against age (Fig 5) show that the slopes are very similar but the intercepts differ by about 20%, indicating that increased prevalence among females was maintained across all ages.

Figure 6a-d presents distributions of percentage of affected monkeys and eyes (6a), mean drusen category (6b), mean age (6c), and number of monkeys sampled (6d) for nine matrilines. Seven additional matrilines were excluded owing to sample sizes of fewer than 10 animals. The abscissa of the first graph is organised by matrilines with decreasing prevalence, and, to aid comparison, this order is maintained in the other graphs in this figure. Several matrilines appeared notable for relatively high percentages of eyes with drusen and higher mean drusen categories. Between 60% and 85% of the monkeys sampled from matrilines AC, 031, 076, and 091 had drusen (Fig 6a). The percentages of eyes with drusen (6a) and mean drusen categories (6b) in these matrilines were also higher than those of other matrilines. Matrilines AC, 031, 076, and 091 were significantly ($p<0{\cdot}001$) different from the others in all three measures of drusen.

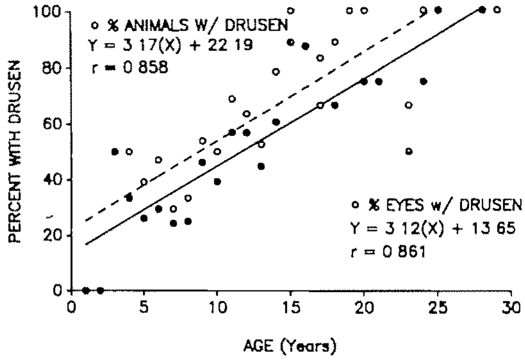

Figure 3 Relationship between age and percentage of eyes and monkeys having drusen. Abscissa is age in years, ordinate indicates percentages (monkeys and eyes) of each age which have drusen. Relationships from linear regression and correlation coefficients are provided in the upper left and lower right corners of the graph.

These four high prevalence matrilines did not differ statistically ($p<0{\cdot}30$) in mean age from the five low prevalence matrilines (Fig 6c). Extrapolation from regression equations (Figs 3 and 4), based on mean ages of the high (mean=11·13) and low (mean=10·75) prevalence matrilines yielded expected differences of 1·25% in prevalence (animals or eyes) and 0·04 in drusen category between the two groups, as compared with differences of 25% and 0·5, respectively, in the data. The only notable difference in sample size (Fig 6d) was the much larger sample from matriline 091. We had access to numerous 091 animals when the troop for which this was the dominant matriline was removed from the island.

Figure 7 presents RMS amplitudes of pattern evoked retinal responses to gratings in two eyes (two animals) differing in drusen size and location. The eye producing the upper curve in this figure had numerous (>15) small drusen scattered throughout the macula. The eye in the

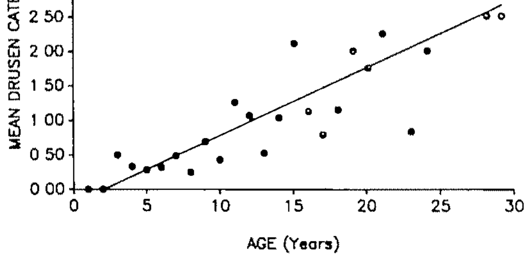

Figure 4 Relationships between age and drusen category. Abscissa is age in years, ordinate indicates mean drusen category Relationships from linear regression and correlation coefficients are provided in the upper left corner of the graph.

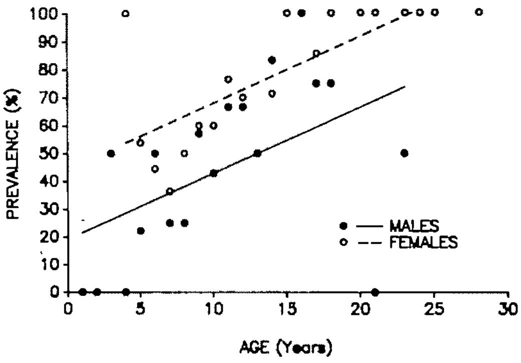

Figure 5 Relationships between age and prevalence for males and females. Abscissa is age in years, ordinate indicates prevalence in percent. Relationships from linear regression are provided in the lower right corner of the graph.

Table 1 Comparisons of drusen in retinas of male and female monkeys

	Males	*Females*	*Total*
Monkeys			
Number	114	132	246
% Total sample	46 3	53·7	100
Mean age (yrs)	10·98	11·4	11·2
Number with drusen**	53	89	142
% of same sex**	46·5	67·4	
% of all with drusen***	37·3	62·7	100
% total sample*	21·5	36·2	57·7
Eyes			
Number	226	264	490
% total sample	46·1	53·9	100
Number with drusen***	81	151	232
% of same sex**	35·8	57·1	
% of all with drusen***	34·9	65·1	100
% total sample*	16·5	30·8	47·3
Mean drusen category***	0·52	1·02	0·79

***p<0·001; **p<0 01; *p<0·05

lower curve had similar quantities of drusen but one large, coalesced druse was centred directly over the fovea. The difference in pattern resolution due to these two drusen distributions is evident. A summary is presented in Table 2 which shows averaged areas (with SD and n) under similar curves for retina and cortex in response to patterns covering 15° and 30° for retinas having >10 and ≤10 drusen. Drusen in most of these eyes were small, scattered, and non-foveal. Retinas with more than 10 drusen performed significantly worse ($p=0·044$) in response to 30° patterns, while marginal ($p=0·64$) differences were seen with 15° fields. Cortical results, however, were not different.

Discussion

In order to identify an animal model for any disease the signs in animals should mimic those of humans. While there is no general agreement on which human signs and symptoms are necessary to diagnose age related macular degeneration,[1] some of the more frequently used are: (*a*) presence of drusen, the typical early lesion; (*b*) relationship of drusen to aging; (*c*) vision loss accompanying drusen; (*d*) late occurrence of exudative or dry disciform lesions.

In addition a number of secondary characteristics have been associated with AMD in humans, including consistently greater prevalence in females than males and relationships between familial (especially maternal) and individual occurrence of the disease.[1,2,18,21-23] The case for a model would be strengthened if all features (including secondary ones) of the human disease could be demonstrated in the animal population. Results from the CPRC rhesus macaque colony suggest that this population has all of the important, drusen related features as well as several of

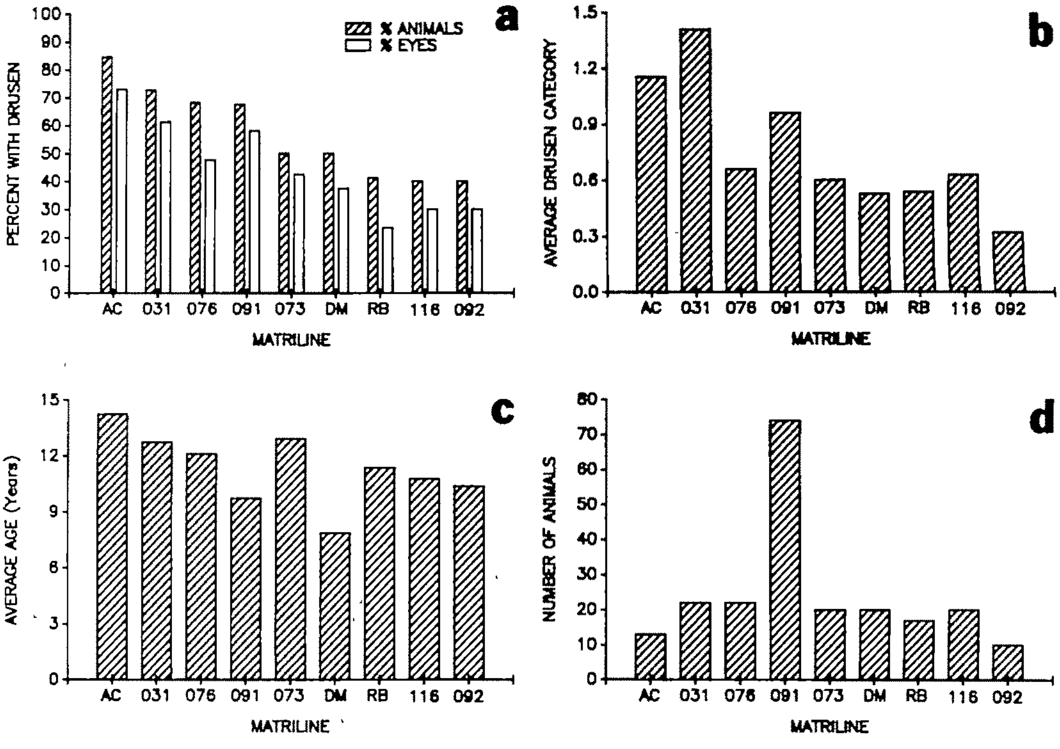

Figure 6 Variation of sample characteristics with matriline. Levels of each ordinal variable are presented versus matriarchal lineages on the abscissa. The matrilines are ordered by decreasing percentage of eyes having drusen in 6a and this order is maintained in 6b–d.

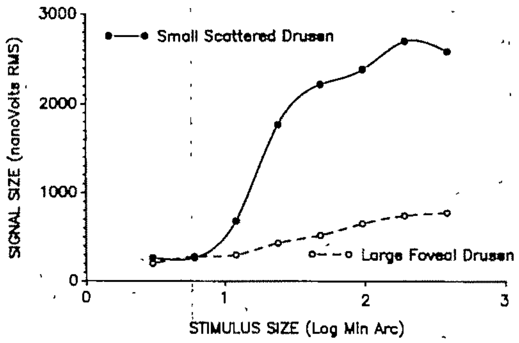

Figure 7 Relationships between resolution and drusen. Comparison of effects of small scattered drusen (solid line, filled symbols) and large foveal drusen (dashed line, open symbols). Data are root mean square amplitudes from retinas on which patterned stimuli subtending the visual angles on the abscissa are projected under visual control.

the epidemiological characteristics of the disease.

The presence of drusen in the eyes of CPRC monkeys and the histopathological similarity of drusen in monkey eyes to drusen in human eyes have been firmly established.[6-11, 13-15, 24] However, in monkey eyes, vacuolated or lipid filled pigmented epithelial (PE) cells can appear virtually identical to drusen.[12, 14, 25] Stafford *et al*[14] noted the difficulty in distinguishing between the two, but Fine and Kwapein[12] speculated that it might be possible to differentiate by the small size and solitary nature of the lipid laden PE cells. We have used the term 'drusen' to refer to the ophthalmoscopic yellowish-white figures in these monkey fundi, which is consistent with its application in clinical medicine. While a small portion of the drusen in our animals have proved to be abnormal PE cells on microscopic examination, a demonstrated increase with age and frequent confluence argue that most are the 'true' drusen we have described at both electron and light microscopic levels.[6]

El-Mofty *et al*[10] found an increase in macular drusen across five increasing age groups of CPRC animals. Bellhorn *et al*[26] found that macular score increased with age among the five age groups into which they divided their sample, but in grades 3 and 4 alone (dependent on drusen) the prevalence appeared to peak at 11–15 years, then decrease in both older and younger animals. Our results establish firm, linear relationships between drusen and aging. The high correlations associated with these relationships, significant intraanimal increases in drusen over one to three years, and previous observations[10] firmly establish that drusen progression in CPRC animals is age related.

Relationships between pattern evoked potentials and visual acuity and dependence of cortical signals on foveal integrity have been established previously.[27-29] The reduced effect of drusen on signals from smaller stimulation fields (greater foveal influence) and unaffected foveally dominated cortical responses is to be expected in these animals whose foveas were mostly intact. We have previously described a non-matriline CPRC monkey whose pattern evoked responses indicated resolution of about 220 minutes of arc in an affected eye compared with about 30 minutes in the unaffected companion.[7, 8] El-Mofty *et al*[10] reported reduction in cone related electroretinograms (ERGs) in affected animals. Bellhorn *et al*[26] found no drusen associated degradation in signals from the eyes or cortices of US animals, with conventional, cone selective, and patterned stimuli. Thus, while loss of retinal resolution capacity is associated with drusen in our small sample of tested CPRC monkeys, the nature of this relationship and of differences between CPRC and mainland monkeys are unresolved.

Table 2 Effects of drusen on electrophysiological indices of visual function

Field size	*Total root mean square signal size* *>10 drusen*	 *<=10 drusen*	*t test p*
	Retina	*Retina*	
30°	3822 (745) (n=7)	6220 (2712) (n=8)	0 044
15°	1433 (666) (n=6)	2337 (703) (n=7)	0 064
	Cortex	*Cortex*	
30°	1675 (264) (n=7)	1553 (703) (n=8)	0·968
15°	945 (302) (n=6)	1154 (842) (n=7)	0·576

A question raised – explicitly or implicitly – in several macaque AMD studies involves the relative paucity of neovascular lesions in monkeys.[10, 26] Stafford *et al* identified seven eyes in four animals among their 574 elderly monkeys (mostly rhesus) having probable choroidal neovascular lesions.[4] These animals were 8–15 dioptres myopic.[14] Myopia has been linked to macular lesions, as these authors note,[14] while AMD correlates with hyperopia in humans.[21-23] We have reported one monkey with a disciform macular lesion ophthalmoscopically identical to those seen in human AMD.[8] The prevalence of severe macular serous and exudative lesions in the Framingham Eye Study was 0·78% (29 of 5253).[18] This compares favourably with 0·7% of Stafford and coworkers,[14] monkeys and 0·4% of our sample. These lesions therefore appear to have been encountered in monkeys at about the same relative frequency as reported in humans. The infrequent observation of end-stage or neovascular lesions in monkeys is probably a function of the relatively few very old monkeys examined.

El-Mofty *et al*[10] found that 25% of the nonselected CPRC monkeys they examined had drusen, which is consistent with our observations on several matrilines (note Fig 4a-b). Comparison of CPRC monkeys with random source monkeys from US mainland facilities is more interesting. Bellhorn *et al*[26] and Stafford *et al*[14] studied relatively large samples ($n=500–600$) and found that only about 6% showed druse-like lesions. If all category 1 (1–5 drusen) CPRC animals are eliminated, comparison with Stafford and coworkers'[14] older monkeys having five or more drusen indicates that 21% of the CPRC monkeys are affected, compared with 6% of their sample of US animals. Bellhorn and coworkers'[26] minimum criterion (<10 drusen) appears to indicate that some 6·1% of their animals had drusen, compared with 57·7% of the CPRC monkeys. Apparently, therefore, the prevalence of monkeys with lesions in the CPRC colony is up to nine times that of monkeys on the US mainland.

CPRC animals differ from those in US facilities in many respects. The CPRC animals are mostly free ranging and are geophagous.[30] They thus may differ from monkeys in US facilities in content of, and/or access to, soil. Several elements have been found to occur in abnormal concentrations in the blood and, notably, drusen of AMD patients.[31-34] CPRC animals are also subjected to lifelong exposure to more direct Caribbean sunlight. A solar irradiation contribution to human AMD, while generally suspected, has been unsupported or supported only indirectly.[35-37] However, recently presented epidemiological evidence implicates exposure to the blue portion of the visible spectrum late in life as a possible risk factor in AMD.[38] Influences due to differences in ingested minerals and elements and differential solar irradiation offer interesting, though speculative possibilities for exploration.

Finally, since no animals have been added to the colony since 1938,[16] all current inhabitants of the island are the progeny of the breeding females surviving the original introduction. While males tend to migrate among social groups, females tend to remain in the group into which they are born.[39] Early introduction of a genetic propensity to develop drusen could, in the succeeding eight to 10 generations, have been transmitted through the closed colony by males yet be more heavily represented in a few primarily affected matrilines. Relationships between maternal lineage and drusen development demonstrated here and the familial – especially maternal – associations observed in AMD in humans[22] implicate this as a potentially important factor in explaining the dramatic difference between drusen prevalence in CPRC monkeys and their US counterparts.

The evidence indicates that all features associated with age related macular drusen in humans can be found in the CPRC rhesus population. Comparisons of these monkeys with those from other populations suggest that this colony is *uniquely* predisposed to develop drusen. While environmental factors may have a role, the associations between drusen development and matriline shown above suggest that a major difference between this closed colony and others surveyed is probably genetic, hence their uniqueness. It appears therefore that CPRC matriline monkeys offer the best human substitute reported so far for the study of spontaneous development of age related drusen, the principal precursor to age related macular degeneration.

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Surgically induced necrotising sclerokeratitis (SINS) – precipitating factors and response to treatment

E O'Donoghue, Sue Lightman, S Tuft, P Watson

Abstract

The clinical features, treatment, and visual outcome of 52 eyes from 43 patients who developed scleritis following surgery were reviewed. In all patients the scleral inflammation developed adjacent to a surgical wound. Ninety six per cent had necrotising disease and 23% also had evidence of secondary posterior scleritis. Many different types of ocular surgery were implicated and the majority (75%) of the patients had two or more surgical procedures before the onset of the scleritis. Although cataract extraction through a limbal incision resulted in the largest subgroup, scleritis also followed glaucoma, strabismus, and retinal detachment surgery. The latent period between surgery and the appearance of inflammation was short (mean 9 months) except for a small group in whom scleritis occurred many years after squint surgery. Sixty three per cent of patients had evidence of a systemic disease. Early diagnosis and aggressive medical treatment significantly improved the visual outcome. The precipitating factors, pathogenesis, and course of this condition are discussed.

Scleral inflammation and necrosis are recognised as rare sequelae to ocular surgery with potentially devastating consequences to the eye.[1-5] Arentsen *et al*[1] described four patients who developed marginal corneal ulceration after cataract extraction, and they distinguished the disease from Mooren's ulcer. Lyne and Lloyd Jones[3] described six patients without a previous history of scleral inflammation who developed scleral necrosis at a surgical wound. They observed that necrosis could develop many months after surgery and could progress to involve the whole of the anterior segment. Salamon and co-authors[4] reported four further cases that developed scleritis, peripheral corneal ulceration and sterile infiltrations around Polyglactin sutures following cataract extraction, whose inflammation settled with intensive topical steroids.

The aetiology of postsurgical scleritis is uncertain.[1,2,6-10] However, it has been noted that scleritis develops more frequently following multiple surgical events than after a single operation.[3] This suggests that the condition may be the result of a hypersensitivity reaction directed against an antigen revealed or altered by tissue injury.

The medical records of all patients from a single clinic population who were documented to have developed postsurgical scleritis or sclerokeratitis were reviewed in order to gain a better understanding of the predisposing factors, both local and systemic, and to examine the outcome of the various treatment regimens that were used.

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Materials and methods

The clinical records were reviewed from a total of 43 patients who had been referred to the scleritis clinic at Moorfields Eye Hospital between 1975 and 1988 and had developed scleritis following ocular surgery. Data were extracted with particular reference to the details of previous surgery, the presence of potential risk factors in the previous medical history, the features of the scleritis, and the treatment required to control the disease. All patients underwent detailed ocular examination using the slit-lamp and indirect ophthalmoscopy. Medical assessment was aimed at the detection of a predisposing disease. Routine investigations included haematology and immunology profiles, serology (VDRL and TPHA), serum uric acid estimation, chest *x*-ray and, in most cases, ultrasonic examination of posterior coats of the eye. Clinical photographs and anterior segment fluorescein angiograms were also reviewed, where available.

Throughout this period the diagnostic classification of scleritis used was that recommended by Watson and Hayreh.[11]

Results

The series consisted of 52 eyes of 43 patients, none of whom had a history of scleritis prior to surgery; 13 were male (mean age at presentation 52·3 years, range 26 to 75 years) and 30 were female (mean age 68·2 years, range 32 to 87 years). Scleritis developed after one operation in 11 patients (25·6%) while the remaining 32 subjects (74·4%) had undergone two or more surgical procedures before the onset of the disease. The nine patients who developed bilateral scleritis had all undergone bilateral ocular surgery. The wound site was intimately related to the site of the subsequent disease process in all the eyes.

The duration of the latent period between surgery and the onset of scleral inflammation varied from 40 years to the first postoperative day (mean duration 39·6 months). However these are weighted by the five cases in whom squint surgery was the only procedure (mean 21·7 years; range 6·5 to 40 years) compared with the remaining 38 cases (mean latency: 5·7 months; range 1 day to 3·5 years).

Necrotising anterior scleritis or sclerokeratitis was identified in 49 eyes (94·2%) (see Figs 1 to 6); the remaining three eyes having nodular scleritis. This is significantly higher than the incidence of necrotising disease in the overall

Table 1 Comparison of scleritis type between 290 consecutive scleritis clinic patients 1986–88 and all whose scleritis followed ocular surgery 1975–88

	Scleritis clinic	*Post surgery*
Diffuse	105 (36%)	0
Nodular	98 (34%)	3 (5·8%)
Necrotising	55 (19%)	40 (94·2%)
Posterior	32 (11%)*	12 (23·1%)†

*Primary disease occurring posterior to equator.
†Secondary involvement of sclera in posterior segment and may be anterior to the equator.

Table 2 Types of surgery

Single procedure (*n*=*11*)	
5	single strabismus corrective procedures
5	unilateral cataract extraction
1	scleral trauma
Multiple procedures (*n*=*32*)	
7	bilateral cataract extraction
8	cataract extraction and secondary ocular surgery (strabismus correction, YAG capsulotomy, ruptured section repair, aphakic retinal detachment repair
5	multiple retinal detachment surgery
3	bilateral trabeculectomy
2	multiple squint surgery
2	anterior segment trauma
1	cataract extraction following herpes zoster ophthalmicus
1	squint preceded by orbital decompression
1	laser trabeculoplasty, trabeculectomy
1	bilateral PI, anterior chamber tap
1	goniotomy, squint, keratoplasty, retinal detachment repair

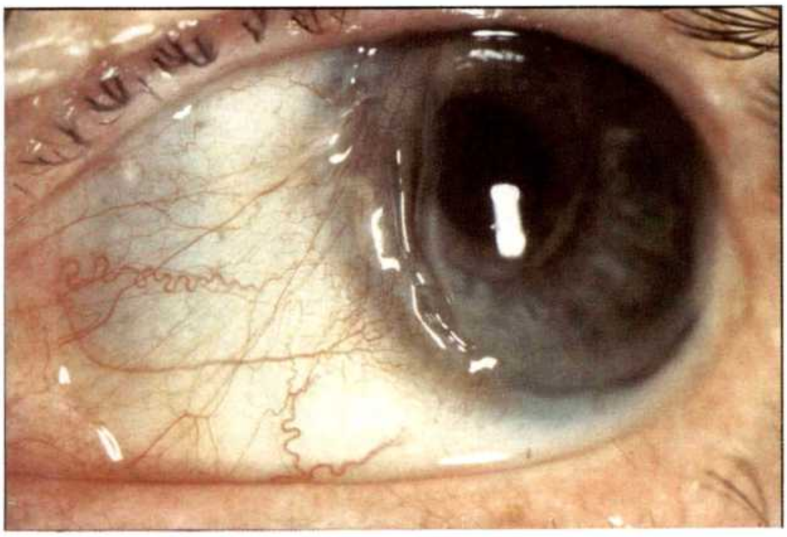

Figure 1 Inactive gutter following control of a sclerokeratitis episode with onset after cataract surgery.

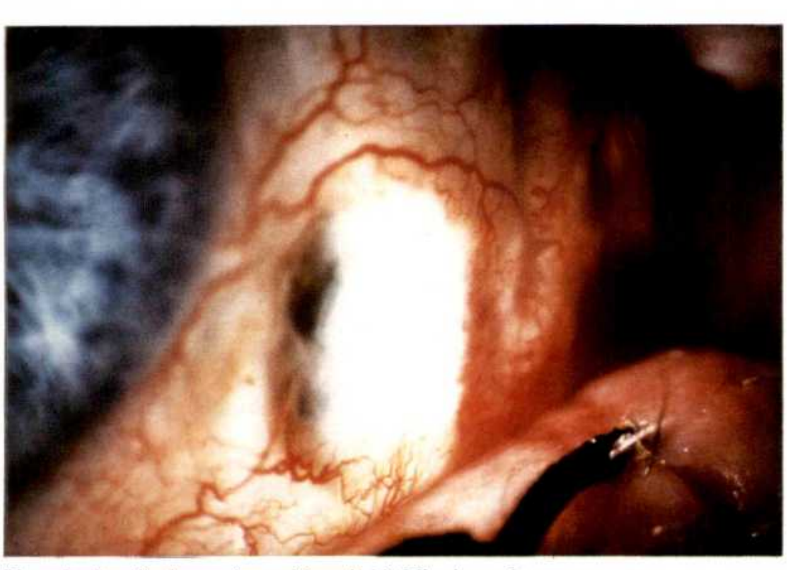

Figure 2 Localised area of necrotising scleritis following squint surgery.

scleritis clinic population[12] (see Table 1) and has major therapeutic implications. However, at initial clinical evaluation less than 60% could be definitely identified as having necrotising scleritis, with the remainder being recognised either by further examination over the following weeks or, in some equivocal cases, the diagnosis was made following anterior segment fluorescein angiography.

The incidence of posterior scleritis was also higher than any previously reported series[13,14] with 12 eyes (23·1%) developing posterior extension of the inflammatory process. Posterior inflammation tended to be localised to the periphery and involved the posterior pole in only two eyes. These findings were confirmed by ultrasonography. All responded to treatment with systemic steroids and posterior scleral inflammation was not a significant contributory factor to visual loss in any of these patients.

A wide variety of surgical procedures preceded the onset of scleritis (see Table 2) which most commonly occurred at the site of incision for cataract extraction (25 eyes, 48%). Of these, 20 (80%) followed limbal incision in which the posterior lip was the main area of involvement, unlike the series of Arentsen *et al*[1] where the anterior lip was mainly affected in all four cases. In these 20 cases the inflammatory process remained confined to the superonasal quadrant in 65%. Five other patients had corneal sections. In two of these, who had necrotising scleritis with minimal corneal involvement, the corneal sutures were found to have entered the sclera. The three remaining patients had predominantly corneal guttering extending from a corneal section with secondary scleral involvement; one patient had serial fluorescein angiographic evidence of gross limbal and scleral ischaemia moving ahead of an advancing corneal gutter (Fig 1). Although the cataract incision was central to the inflammatory process in all 25 cases it is clear that minor subsequent surgical procedures (suture removal, YAG capsulotomy and repair of wound leak) were the provocative insult in six of these.

Nine patients (12 eyes) developed scleritis at the site of previous squint surgery. Unlike the patients so far discussed, in whom the onset of scleritis shortly followed the surgical insult, five of these patients had a single strabismus correction procedure in childhood with onset of scleral disease many years later (mean interval 21·7 years) (Fig 2). Of these five patients, four were female and four had previously undiagnosed immune abnormalities. This included two who were found to be rheumatoid factor positive and who later developed rheumatoid arthritis, and two whose scleritis was preceded by seronegative acute polyarthropathy and who were found to have high circulating immune complexes but no further disease manifestations. The four other patients underwent multiple surgery in adulthood with strabismus surgery being the final procedure (that is, for diplopia following cataract extraction) provoking localised scleritis after a much shorter interval (mean 10 weeks). The area surrounding lateral rectus insertion was selectively involved in nine of 12 eyes (75%) despite seven having had concurrent surgery to ipsila-

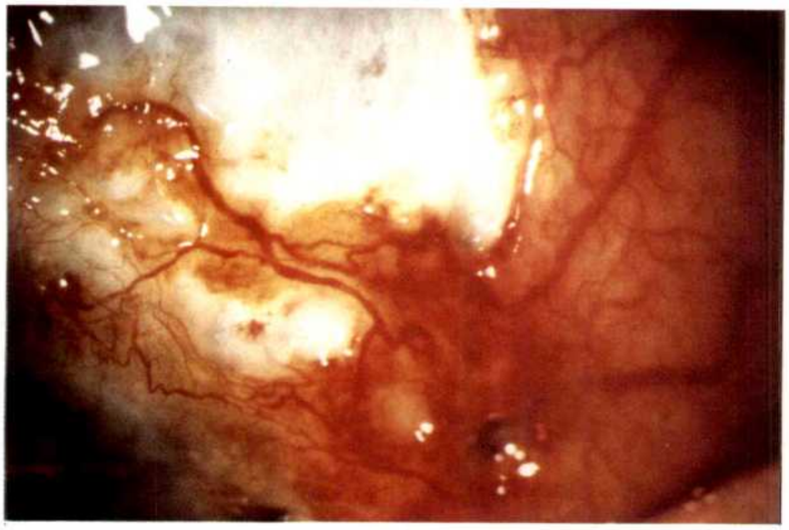

Figure 3 Scleritis following trabeculectomy showing both early and advanced areas of necrosis. A provisional diagnosis of Wegener's granulomatosis was subsequently confirmed.

teral medial rectus suggesting increased vulnerability of the vascular bed in this region.

Seven cases of necrotising inflammation followed retinal detachment surgery. In four of these scleritis occurred at the explant site and the subsequent management included removal of explant in three cases with rapid resolution of the scleritis. Two further cases occurred at vitrectomy entry sites and another patient developed scleritis at the site of previous cataract surgery within weeks of an uncomplicated repair of an aphakic retinal detachment.

Four patients with glaucoma presented at a mean interval of 12 months following trabeculectomy with an inflamed non-filtering bleb and rapid progression of localised necrotising scleral disease (Fig 3). Scleritis was also seen in one case after surgical iridectomy.

Table 3 Associated disease

4	diabetes mellitus		
5	thyroid disease	4	hyperthyroid (2 also with collagen disease)
		1	hypothyroid
14	collagen disease	7	rheumatoid arthritis
		3	Wegener's granulomatosis
		1	polyarteritis nodosa
		2	seronegative polyarthropathy
		1	polymyalgia rheumatica
1	hyperuricaemia		
1	herpes zoster ophthalmicus		
13	no known associated disease		

Adequate documentation of associated systemic disease was available for 36 patients (Table 3). In 11 of these 36 patients no associated disease had been noted prior to the onset of scleritis but was revealed by subsequent investigation. Fourteen patients had serological and/or clinical evidence of a systemic collagen disease, five had a thyroid disorder (two in association with collagen disease), four were diabetic and one patient was hyperuricaemic. No evidence of any systemic disorder was found in 13 other patients and in the remaining seven cases insufficient data precludes comment.

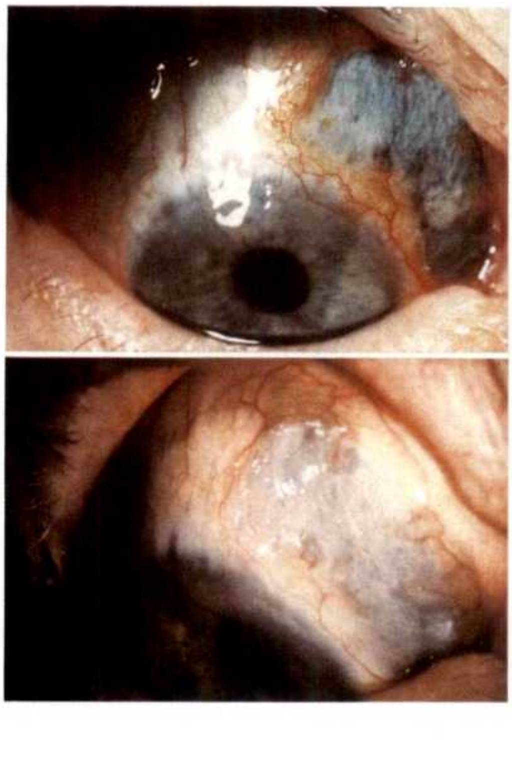

Figure 4 Upper figure illustrates necrosis with onset 4 weeks after removal of a subconjunctival nylon suture (cataract extraction was performed 5 months previously). Lower figure shows early resolution 9 days later on high dose systemic steroids.

Postoperative infection and herpes zoster ophthalmicus were implicated in one case each. As found in earlier studies[1,3,9] the use of a specific suture material could not be related to the development of the disease.

The scleritis was controlled in all patients and no eyes were excised. Non-steroidal anti-inflammatory agents were sufficient to control the disease in only three patients despite their use as the initial treatment regimen in half of the group. For 40 patients high dose systemic steroid therapy (60 to 80 mg daily) was an essential part of their management and was usually followed by rapid resolution and healing (Fig 4); all needed low dose maintenance therapy for periods ranging from 2 months to 6 years. In addition to oral prednisolone, 11 patients were given at least one pulse of intravenous methylprednisolone (500 mg) and 15 patients needed adjunctive therapy with immunosuppressive agents – oral or intravenous cyclophosphamide or oral azathioprine (Table 4). For three of the four patients with retinal detachment with necrosis at the explant site control was only achieved following high dose systemic steroid treatment *and* the removal of the explant. Perforation through necrotic sclera or cornea occurred in eight (Fig 5) patients necessitating surgical excision of necrotic tissue and tectonic reconstruction (six corneoscleral grafts, one scleral graft, one corneal patch graft).

Reactivation of the disease requiring re-treatment was seen in 16 patients either on reduction of steroid dosage shortly after the acute stage or, in some patients, after a long remission off all treatment. Those patients who had recovered from SINS and required further ocular surgical procedure were given perioperative pulsed methylprednisolone to protect against recurrence of necrotising disease.

Table 4 Treatment required to control disease

Non-steroidal anti-inflammatory agents	3
High dose systemic steroids	40
Pulsed intravenous steroids	11
Oral cytotoxic agents	15
Surgical reconstruction	8
Removal of surgical explant (retinal detachment)	3

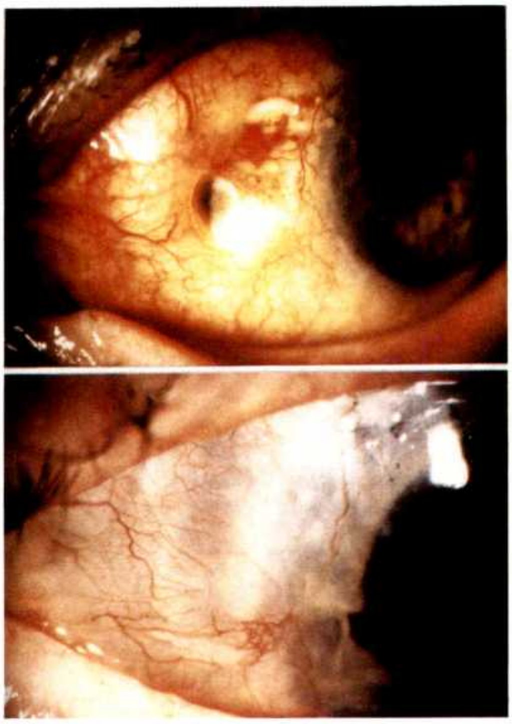

Figure 5 Upper figure: scleritis close to limbal section. Resolution with a short course of high dose systemic steroids was sustained for 1 year when recurrence led to perforation requiring scleral patch graft and treatment with cyclophosphamide and pulsed methylprednisolone (lower figure).

There was a clear-cut relationship between aggressive early medical treatment and successful visual outcome (see Table 5). Of the 24 patients who had high dose systemic steroid treatment within 1 month of the appearance of symptoms the mean visual loss was Snellen equivalent 0·5 lines (range 0 to 3 lines lost). In seven other patients with necrotising disease there was an interval of at least 3 months between onset and the initiation of steroid treatment to achieve control; these patients suffered profound and permanent visual loss – five eyes became phthisical, two eyes lost five Snellen lines. The mean follow-up period for these two groups of patients ($n=31$) is 5·2 years. Analysis of 12 other patients was not possible because of insufficient data, loss to follow-up or the recent onset of the disease.

Table 5 Long term visual outcome related to the interval between onset of scleritis and initiation of high dose steroids

Interval	*Number of patients*	*Mean Snellen loss (>5 year follow-up)*
<1 month	24	0·5 lines (range 0–3)
>3 months	7	7·0 lines (range 5–9)

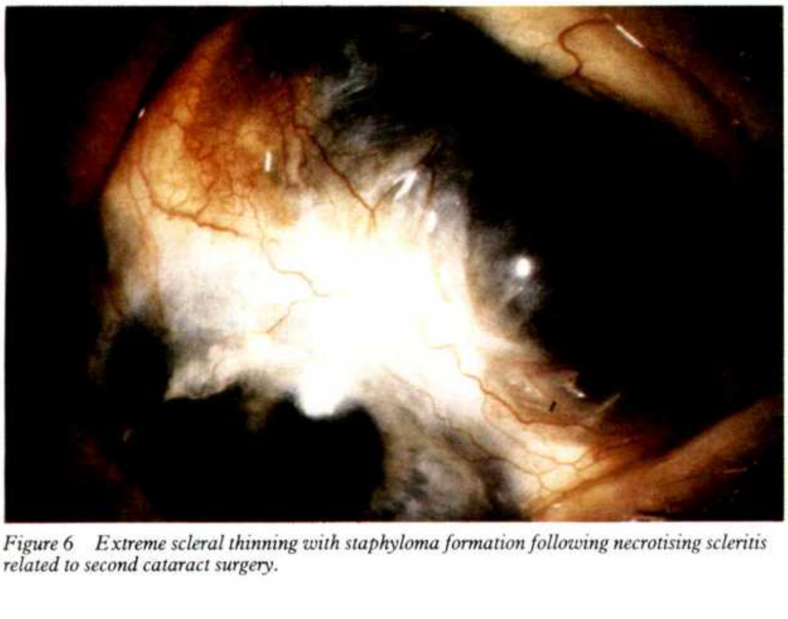

Figure 6 Extreme scleral thinning with staphyloma formation following necrotising scleritis related to second cataract surgery.

Discussion

These results demonstrate that scleral disease developing as a complication of a surgical procedure is most likely to be of the necrotising type. Necrosis is four times more common in the surgical group than in a non-surgically induced scleritis clinic population. Anterior segment fluorescein angiography demonstrates that the vascular closure is limited to the immediate vicinity of the wound in most cases. Seventy five per cent of patients developed disease after multiple ocular surgical procedures, some of them minor, with a mean interval of 9 months and a 40% association with a predisposing medical disorder. The remaining population developed disease after a single surgical episode with a mean interval of 9·5 years and a 90% association with a predisposing medical disorder. This group further differed from the multiple surgery group in having a fivefold greater incidence of background collagen disorder where scleritis tended to be but one of a number of the acute manifestations of underlying systemic disease.

Overall, 63% had an underlying medical disorder of which the commonest group was connective tissue disease. Eight patients had evidence of organ-specific autoimmune diseases such as thyroid disorder or diabetes; 70% of patients were female which is in keeping with the increased incidence of autoimmune diseases in females. The exact relationship of the medical disorder to the development of postoperative scleritis is unknown but systemic vasculitis is a feature of the collagenoses and this can occur in the blood vessels of the deep episcleral venous plexus. Moreover, patients with one autoimmune disease have an increased risk of developing other diseases of the autoimmune group, suggesting that there may be two separate aetiological factors predisposing to the development of the disease. In the first group, the blood vessels themselves may be affected as a primary event and in the second there is a tendency to develop organ specific autoreactivity. Complicating both of these factors is the effect of at least temporary localised relative ischaemia as a consequence of the surgical incision.

The time of onset of scleral necrosis in these patients is very interesting. In most cases it does not occur in the immediate postoperative period, suggesting that primary vascular closure and ischaemia alone are unlikely to be important initiating events. In addition the rapid response to immunosuppressive drugs implies that the immune system is actively involved at least in the perpetuation and maybe the initiation of the inflammatory response. Neither corticosteroid drugs nor cyclophosphamide are selective immunosuppressants and therefore do not give any clues as to the involved arm of the immune system, with both T cells and B cells being affected by these drugs.

The histological appearance at the edge of a lesion of necrotising scleritis is said to be of a delayed type of hypersensitivity response,[7] which is known to require the presence of sensitised CD4+ T cells. The antigen in the vicinity of the sclera to which these T cells become sensitised has not been identified, but it is possible that either the surgical trauma or the temporary ischaemia alters or exposes tissue antigens to which the immune system is not normally exposed and which are therefore recognised as foreign. Circulating antibodies to scleral collagen are rarely detected in these patients, but circulating immune complexes have been noted in some. The relevance of this is unknown but may contribute to the vasculitis after its initiation. Since the pathological process is usually that of a necrotising inflammation, its pathogenesis may be different from the more usual types of scleritis and subclinical ischaemia may be a pivotal factor. It is likely that ischaemia plays an important role in the scleritis that follows encirclement for retinal detachment since removal of the buckle usually results in reduction in and healing of the scleral disease. Likewise significant local ischaemia is a known complication of squint surgery, and in our patients developing scleritis following cataract surgery it is much more frequently associated with limbal approach than following corneal section – perhaps reflecting the greater relative vascular disruption.

It is also possible that the immune response is triggered elsewhere and becomes manifest in the eye for other reasons. (This would seem to be the case in those patients who had an interval of many years between surgery – usually a single uncomplicated procedure – and onset of scleritis, in most of whom the ocular inflammatory episode was almost concurrent with other early systemic manifestations of immune disorders such as rheumatoid arthritis, Wegener's granulomatosis, or polyarteritis.)

First, immune complexes which are formed as a consequence of a problem elsewhere in the body could be deposited in the deep episcleral blood vessels which are affected by the surgical procedure. This could subsequently initiate the inflammatory response in the eye over a period which would appear unrelated in time and place to the initial stimulus. Alternatively, there could be molecular mimicry/cross-reactivity between an ocular antigen and either a tissue antigen elsewhere in the body or a microbial antigen (that is, ankylosing spondylitis and *Klebsiella*; experimental allergic uveitis (EAU) and fungus).[15 16]

Whatever the aetiology of this devastating scleral inflammation, the paramount message from the results presented here is that appropriate treatment must be started as early as possible. Non-steroidal anti-inflammatory agents are not usually effective in the face of this disease so that immunosuppressive treatment with high dose corticosteroids and cytotoxic drugs as necessary should be used at presentation and their instigation should not be delayed. Should the disease progress in spite of adequate immunosuppression surgical replacement of damaged tissue must be considered. With a greater understanding of the immune mechanisms involved, it may be possible to use more selective immunosuppressive agents in the future and spare these patients some of the side effects of this necessary treatment.

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Is there a genetic basis for Fuchs' heterochromic uveitis? Discordance in monozygotic twins

N P Jones, A P Read

Abstract

One pair, and probably two pairs, of monozygotic twins are reported with discordance for Fuchs' heterochromic uveitis (FHU). Regular Mendelian inheritance of this disease is now proved to be impossible. The heritability of FHU is low and may be zero. The possibility of any genetic predisposition to the disease and its association with 'simple' heterochromia are discussed.

Fuchs' heterochromic uveitis (FHU) is a chronic, indolent uveitis of unknown aetiology first described comprehensively by Ernst Fuchs in 1906.[1] The occasional concurrence of FHU in more than one member of the same family has been reported[2-5] and the possibility of a genetic aetiology, usually described as an autosomal dominant trait with low penetrance, has been discussed on several occasions. In 1955, Franceschetti,[6] having reported a large series of 62 patients with FHU and established the modern criteria for diagnosis, concluded that 'If one day we have the good fortune to find identical twins with Fuchs' syndrome, we hope it will then be easier to answer the difficult question of the role of a genetic factor in complicated heterochromia'. Almost immediately, FHU coexisting in a pair of monozygotic twins was described,[7] and the possibility of a genetic factor was further strengthened. Family studies on a cohort of 103 patients with FHU are reported here, including case reports of discordance of FHU in monozygotic twins. The implications of these findings on a genetic theory for FHU are discussed.

Patients and methods

From 1987 all new and old patients attending the outpatient department at Manchester Royal Eye Hospital with a definite or suggested diagnosis of FHU were referred to one of us (NPJ). Of these, 103 patients were considered to fulfil the diagnostic criteria for FHU. As part of a comprehensive history and examination these patients were questioned on their family history and a family tree was constructed. Any history of possible heterochromia or inflammatory eye disease was noted. Where possible allegedly affected family members were examined. DNA analysis on a pair of monozygotic twins was performed.

Results

In 13 cases the family history was incomplete or unknown due to lack of knowledge on the part of the patient (two being adopted). Of the remaining 90 patients (who had a total of 601 first degree relatives) 84 (93·3%) had no family history of heterochromia or ocular disease. Six patients (6·7%), however, each thought that one other family member had heterochromia. For geographical and other reasons it was possible to examine only two of these six suggested cases. In both instances there was unilateral sector hyperpigmentation, no sign of past or present intraocular inflammation, and otherwise normal ocular examination. This cohort of 103 patients included two who had a monozygotic twin, but no dizygotic twins. Both are reported below.

Case reports

CASE 1

The patient, a 51-year-old woman, presented with a history of gradual loss of vision on the left side. She was aware of heterochromia affecting the left side which had been present since birth. This eye was known to be amblyopic but further visual loss had occurred.

On examination of the left eye there were numerous stellate keratic precipitates scattered evenly over the whole posterior surface of the cornea, with fine interconnecting fibrillary deposits. There were few cells in the anterior chamber and barely detectable flare. The right iris had a normal architecture and was light brown (Fig 1). The left iris was macroscopically blue, the anterior border layer pigment had entirely disappeared, and this layer was grossly atrophic (Fig 2). The iris stroma was also markedly atrophic with obvious thinning and some visibility of pigment epithelium from the anterior aspect. The iris pigment epithelium was clearly abnormal and there were large scattered transillumination defects, mainly peripheral but also involving the pigment ruff. The pupil on this side was slightly irregular, but there were no posterior synechiae. A posterior subcapsular cataract was present, and vitreous cellular activity and condensations were visible. There were no fundal lesions. The diagnosis of FHU was made.

The patient was one of triplets. There was no history of maternal illness in pregnancy, and the patient was delivered vaginally at term without complications. One further child, a girl, was delivered without mishap but a third female was stillborn and small.

The surviving twin was examined. The eyes were completely normal. The irides were a very similar colour to the normal right iris of the patient; stromal architecture and pigmentation were symmetrical and normal. There was no evidence of past or present intraocular inflammation and the lenses were clear. There was therefore no evidence of FHU (Figs 3 and 4).

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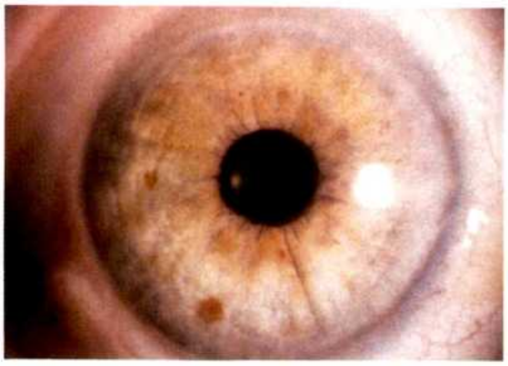

Figure 1 Case 1. The twin with Fuchs' heterochromic uveitis, normal right eye.

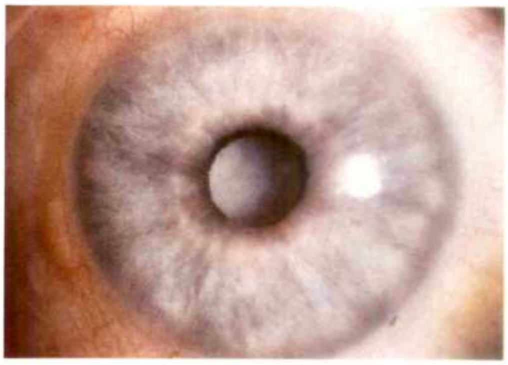

Figure 2 Case 1. The twin with Fuchs' heterochromic uveitis, affected left eye.

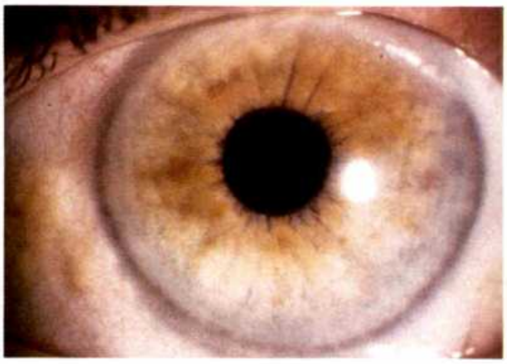

Figure 3 Case 1. The unaffected twin, right eye.

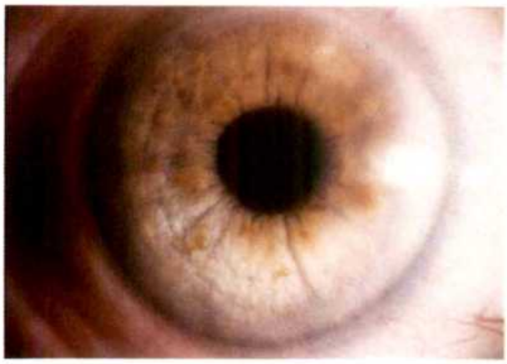

Figure 4 Case 1. The unaffected twin, left eye.

The twins were facially very similar even at 51 years of age, and in fact the patient's heterochromia had been a useful distinguishing feature in childhood. DNA analysis was performed by means of the minisatellite probe 33·6, which showed that each twin had 25 clearly visible bands, which were in identical positions.

CASE 2

This female patient presented at the age of 69 with a history of floaters. She was aware of her profound heterochromia, which had been present since birth. On examination she had clear evidence of right-sided heterochromic uveitis, with widespread stellate keratic precipitates and typical iris atrophy with hypochromia. There was incipient band keratopathy. The affected iris was blue, the unaffected one being light brown. The lens was clear but there was cellular activity in the anterior vitreous.

The diagnosis of FHU was made. The patient had no family history of heterochromia and was one of twins. The maternal pregnancy and delivery had been uneventful. The twin had unfortunately died recently at the age of 72, and a planned ocular examination and DNA analysis had not been possible. Anecdotally the surviving twin was convinced both of their monozygosity and their discordance for heterochromia. The heterochromia had apparently been the only distinguishing feature in childhood.

Discussion

The issue of a possible genetic basis for FHU has been raised on several occasions in the past. Evidence for this might be sought from twin studies, from evidence that FHU tends to be familial, or from evidence of a relationship to more clearly defined genetic conditions.

TWIN STUDIES

Makley[7] found a pair of presumed monozygotic twins in 1956 who were concordant for FHU. The possibility of a non-genetic aetiology still existed of course, as the twins had occupied the same uterus simultaneously. However, our finding of one, and probably two, pairs of discordant monozygotic twins now formally disproves any wholly genetic aetiology for FHU. The twins in case 1 shared all 25 bands seen with DNA fingerprinting. The chance of dizygotic twins sharing one band is about 0·6,[8] and the chance of sharing all 25 is $(0{\cdot}6)^{25}$ or 3×10^{-6}. Thus they are monozygotic, and they are certainly discordant for FHU. Probably the twins in case 2 were also monozygotic, since the heterochromia in one of them was reportedly the only distinguishing feature in childhood.

EVIDENCE FOR FAMILIAL TRANSMISSION

Some authors[9 10] have described FHU as a dominant condition with low penetrance, but the reported series show that in the vast majority of instances it is not familial. In the literature to date approximately 1800 cases of FHU have been reported.[11-16] Familial cases have been published in a few instances, but it should be noted that selective reporting of familial transmission[1-5] may overestimate the possibility of heritability. The reports of familial transmission include: two sisters[2]; a mother and daughter[3]; an uncle and nephew[4]; two sisters[5]; and five further families.[13 17] In 1956 Makley[7] reported the coexistence of FHU in a pair of twins, who were judged to be monozygotic on the basis of blood grouping and hand-print comparison. Loewenfeld and Thompson[11 12] have critically reviewed the earlier reports above[2-5 7] and many other reported familial cases; only those cited above seem likely to be genuine. The proportion of familial cases is certainly <1·0% and does not provide adequate evidence of direct heritability of FHU.

RELATIONSHIP TO GENETICALLY DETERMINED CONDITIONS

There is a possibility that both sector hyperpigmentation of the iris, and heterochromia without inflammation ('simple' heterochromia) may be transmitted as a genetic trait.[18 19] Could such a mechanism be of relevance to FHU? Patients with FHU can have either congenital or acquired heterochromia.[6 16] If the FHU itself were congenital in those with congenital heterochromia, then such patients would present earlier than those with acquired heterochromia. This, however, is not the case.[16] In this series of 103 patients the age at diagnosis of FHU in those with congenital heterochromia is, paradoxically, actually later than that for those with acquired heterochromia (mean 41·4 years and 33·7 years, respectively). Thus patients with congenital heterochromia must have a latent period without inflammation before FHU develops. At this time, therefore, they have 'simple' heterochromia. It should be considered a possibility that simple heterochromia is transmitted as a genetic trait, and that FHU arises as a complication in some (probably most) of these.

Heterochromia can occur as a dominant condition, either as part of the Waardenburg syndrome or, more questionably, in isolation.[19] In the Waardenburg syndrome the underlying cause lies in the neural crest.[20] In our series there was anecdotal evidence of heterochromia in six out of 601 first degree relatives. In the two relatives we were able to examine there was unilateral sector hyperpigmentation. The heterochromia seen in Waardenburg syndrome is also often unilateral and segmental (Newton V, personal communication). However the underlying pathology must be quite different because FHU is not a complication of Waardenburg syndrome.[12] True FHU has not been described in association with the Waardenburg syndrome and it appears unlikely that the two conditions are related.

Conclusions

It is clear that FHU and its antecedent heterochromia do not show regular Mendelian inheritance. Genetic predisposition does not play a large part in the overall risk of FHU. The very low rate of familial concurrence, and the lack of temporal relationship between the onset of heterochromia and of the FHU in those with congenital heterochromia, suggest that at least two rare events are required, one (which may be intrauterine) to cause the heterochromia and a second event to trigger the progression to FHU.

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Autofluorescence of the crystalline lens in early and late onset diabetes

J M Sparrow, A J Bron, N A Phelps Brown, H A W Neil

Abstract

Blue/green autofluorescence (excitation around 420 to 430 nm, emission around 520 nm) of the crystalline lens has been studied by an in vivo photographic method in two populations of diabetics and controls. The populations consisted of a geographically based survivor group of 161 mixed early and late onset diabetics (and 133 non-diabetic controls) and a second group of 104 early onset insulin dependent diabetics (and 138 non-diabetic controls), the latter all with non-cataractous lenses. Powerful associations ($p<10^{-6}$) were found between the presence of diabetes and increased lenticular autofluorescence in both populations. Among the mixed diabetics diabetic type was a significant factor after accounting for the effects of age and diabetic duration. In the early onset group (clear lenses) a powerful association existed between autofluorescence and diabetic duration ($p=0{\cdot}000011$) after allowing for the effect of age, while in a subgroup of late onset diabetics with clear lenses this effect was modest ($p=0{\cdot}015$). In the early onset diabetic group diabetic retinopathy ($p=0{\cdot}0064$) was associated with increased lenticular autofluorescence after allowing for the effects of age and diabetic duration. In addition a powerful interaction between diabetic duration and the presence of diabetic retinopathy ($p<10^{-6}$) was found in this subgroup. Among the geographically based population of diabetics, increased nuclear brunescence was powerfully associated ($p<10^{-6}$) with increased autofluorescence after allowing for the effects of age, diabetic duration, and type of diabetes. This association was not found in the non-diabetic population. Non-enzymatic glycosylation of lens proteins should be considered as a possible mechanism of production of the fluorogen with emission around 520 nm.

Diabetes is an accepted risk factor for cataract formation[1-3] and it has been estimated that 12% of cataracts extracted in Britain can be attributed to this risk factor alone.[3] Cataract surgery occupies more than 40% of the surgical workload of ophthalmologists,[4] which implies that mechanisms of cataract formation in diabetes refer to more than 5% of all eye surgery. Study of these mechanisms by simple clinical methods can provide clues to more basic events taking place in the diabetic lens and could be of value in the development and testing of treatment strategies designed to diminish lenticular damage in the clinically and economically important disease combination of diabetes and cataract.

The adult human lens contains molecules that exhibit autofluorescence.[5,6] This phenomenon can be elicited at various wavelengths, some in the visible spectrum (blue/green fluorescence may be observed using the blue light of a standard slit-lamp biomicroscope, excitation around 420 to 430 nm, emission around 520 nm)[7-11] and some in the ultraviolet spectrum (UV/blue, excitation around 360 nm, emission around 440 nm).[6,8,12-15] In vitro 'purple' fluorescence (290/340 nm)[6,12] (probably due to tryptophan) and longer wave fluorescence, red (647/672 nm), near-red (568/633 nm), and orange (568/591 nm) have also been reported.[16] Autofluorescence of the lens increases with age in normal individuals[5,8,9] and is increased in nuclear cataract.[6,8,9,16,17] Blue/green fluorescence is increased in diabetes[7,10,11,18] and this increase has been noted to be duration dependent[11] and related to diabetic control.[18] The nuclear and perinuclear cortical regions of the lens show the most intense blue/green autofluorescence[9,11,19] and an assumption that a single blue/green fluorophor exists is supported on theoretical grounds by Beer–Lambert analysis of in vivo fluorophotometric scans.[20] The fluorogen responsible for the UV/blue fluorescence is closely associated with the yellow pigment of ageing and nuclear brunescent cataract,[17,21-23] and may be derived from tryptophan, possibly photochemically,[8,14] or by non-enzymatic glycosylation of lens proteins.[21,22,24,25] In diabetes fluorescent products of non-enzymatic glycosylation of 'browned' protein have been demonstrated, with excitation and emission maxima around 370 nm and 440 nm respectively.[26,27] The longer wavelength blue/green fluorogen (studied here) may be derived from the shorter wavelength fluorogen.[8,19]

Methods

STUDY POPULATIONS

Two groups of diabetics and controls have been studied.[28] Briefly the survivors of a geographically based population sample of diabetics[29] and controls, group matched for age and sex were recruited. These diabetics will be referred to as the 'mixed' diabetic population, the age distribution of these diabetics and controls being shown in Fig 1. The majority of the mixed diabetics were in fact late onset non-insulin dependent diabetics, and from this mixed group a subgroup of exclusively late onset diabetics was withdrawn for analysis. A second population of early onset diabetics with non-cataractous lenses was also recruited, these individuals being identified in a general diabetic outpatient clinic, a paediatric diabetic outpatient clinic, and an ophthalmological diabetic outpatient clinic. This second

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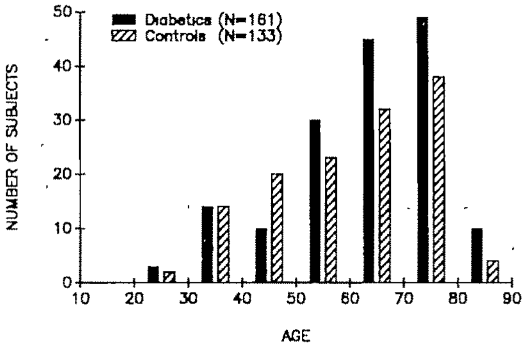

Figure 1 Age distribution of the 'mixed' diabetic population and non-diabetic controls.

population will be referred to as the 'early onset' diabetics. Early onset diabetes was defined as diabetes requiring insulin treatment from diagnosis in patients with an age of onset ≤30 years, and all others were regarded as late onset (non-insulin dependent) diabetics. The non-diabetic control population for the early onset group consisted of individuals with non-cataractous lenses selected from the above control group, supplemented by individuals with clear lenses and no anterior segment disease who were recruited from ophthalmological casualty and outpatient departments. The age distribution of the early onset diabetics and controls is given in Fig 2. (In the case/control comparisons between these diabetics and non-diabetics, statistical compensation for imperfect age matching was achieved by treating age, a potentially confounding variable, as a covariate.) Clear lenses were defined by the Oxford Clinical Cataract Classification and Grading system[30 31] as follows: Nuclear scatter and nuclear brunescence up to and including Grade 2 were allowed, spoke opacities and waterclefts of Grade 1 were allowed, but all lenses with any anterior or posterior subcapsular opacities were excluded. Minor lens changes such as isolated vacuoles, retrodots, and focal dots were permitted. For all participants a minimum of 2 weeks from exposure to fluorescein (intravenous or by drops) was considered reasonable for inclusion in the study.

SUBJECT EXAMINATION

Approval for the study was obtained from the Central Oxford Research Ethics Committee (ref no 1211). Following recruitment, informed verbal consent was obtained from each subject.

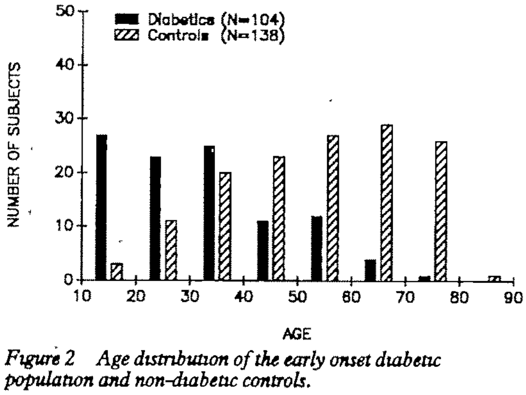

Figure 2 Age distribution of the early onset diabetic population and non-diabetic controls.

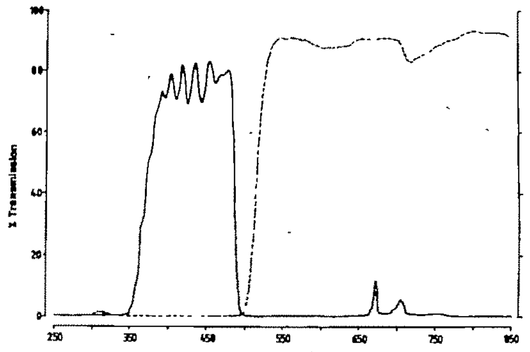

Figure 3 Transmission characteristics of the excitation (__) and barrier (___) filters used for recording lenticular autofluorescence.

All participants were examined and photographed by a single examiner (JS) at the Oxford Eye Hospital. The assessment consisted of the administration of a questionnaire and a full ocular examination (under mydriasis) with special reference to the lens of the eye. Lens changes were quantified by slitlamp examination using the Oxford Clinical Cataract Classification and Grading System,[30 31] and autofluorescence, Scheimpflug[32-34] and retroillumination[35] lens photography were performed at the end of the assessment.[28 36]

PHOTOGRAPHIC RECORDING OF LENTICULAR AUTOFLUORESCENCE

Lenticular autofluorescence was photographed using a slightly modified Zeiss anterior segment camera. The system contains a blue excitation filter (Balzers, interference type), in the illuminating beam, and a yellow barrier filter (Wratten 12) in the light path before the photographic emulsion. The filters were chosen in order to examine the visible range lenticular autofluorescence seen in lenses of diabetic subjects,[7 9-11] the transmission characteristics of the filters being illustrated in Fig 3. The fluorescence recorded has an excitation wavelength of around 420 to 430 nm, and an emission wavelength of around 520 nm. The arrangement of the filters was such that reflected blue light from the eye could not reach the light sensitive film, only light emitted by fluorescence was able to pass through the barrier filter and expose the photographic emulsion. A small amount of 'leaked' red light (between 660 and 720 nm) was able to pass through both filters. This 'contaminating' red light is seen in the image as a small specular corneal reflection of the flash light source (Fig 4). The spectral sensitivity of the black and white film used in this study (Ilford XP1) was low in the region of this contaminating red wavelength.

IMAGE ANALYSIS OF AUTOFLUORESCENCE PHOTOGRAPHS

The intensity of the lenticular autofluorescence was measured by examining digitally a rectangular sample of grey levels from the autofluorescence photographs as shown in Fig 4. The rectangle analysed covered part of the fluorescing lens and part of the background of the photographic image, care being taken to avoid

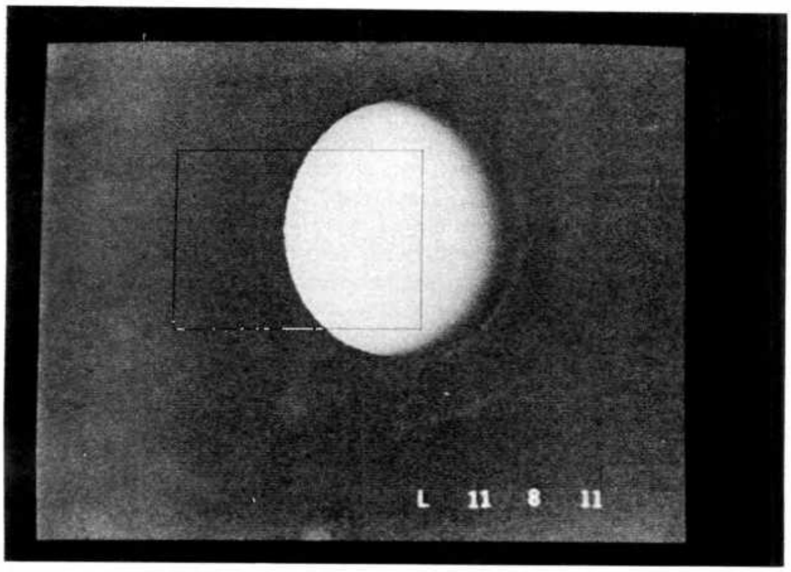

Figure 4 *Autofluorescence image as seen on the video screen of the digital image analysis system. The rectangular 'area of interest' is the region used for making the fluorescence measurement. (Reproduced from* Eye *with permission of the Editor.)*

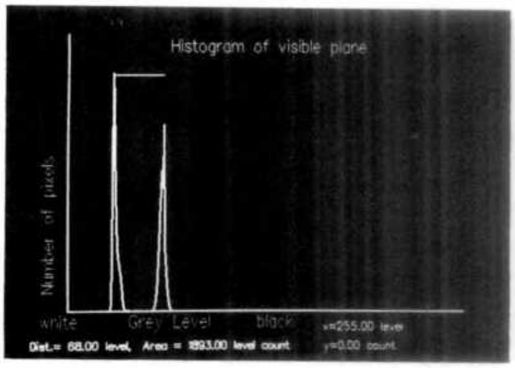
Histogram of visible plane
Number of pixels
white
Grey Level
black
x=255.00 level
y=0.00 count
Dist.= 68.00 level, Area = 1893.00 level count

Figure 5 *Histogram of the grey levels from the rectangular 'area of interest' indicated in Fig 4. The bimodal distribution represents the fluorescing lens (light peak) and the image background (dark peak). The measure (arbitrary units) is taken as the difference between the two peaks of the (standardised) histogram. (See ref 37 for details of image analysis system.) (Reproduced from* Eye *with permission of the Editor.)*

the corneal specular reflex. The frequency distribution of the pixels across the grey scale within the rectangular 'area of interest' produced a bimodal distribution (Fig 5) the 'white peak' representing the fluorescing lens, and the 'dark peak' representing the background. The measure used for the intensity of the autofluorescence was the difference between the two peaks of the standardised histogram. The units of fluorescence were determined partly by technical constraints and partly for convenience resulting in a total range of between 0 and 130 arbitrary units. In a dilution experiment the fluorescence units were found to follow a sigmoid curve when plotted aginst the logarithm of fluorescein concentration ($R^2=0{\cdot}99$ for third order polynominal regression, $n=84$ samples measured).[28] The linear portion of the sigmoid curve however lay within the range 10 to 110 units, which is the range covering the vast majority of measurements made in the present work (Figs 6 and 7). The details of the digital image analysis system have been described previously.[37]

REPEATABILITY OF THE AUTOFLUORESCENCE MEASURE

The repeatability of the method for measuring lenticular autofluorescence was assessed by examining repeat images of the same eyes taken at two separate photographic sessions several months apart. A population of differences between initial and subsequent assessments was obtained from analysis of 60 images of 30 eyes (half were left eyes and half were right eyes). The average difference between initial and subsequent measurements was negligible (0·37 fluorescence units). Assuming the 'true' value for a particular lens to be the mean of the two measurements, the standard deviation (SD) of the errors away from the 'true' value describes the accuracy of the method. Assuming a normal distribution (this was approximately true) there is a probability of 0·95 that any individual error away from the 'true' value will lie within the range ±(1·96 SD).[38] The relevant range for errors away from the 'true' value was ±15 fluorescence units. In order to ensure better

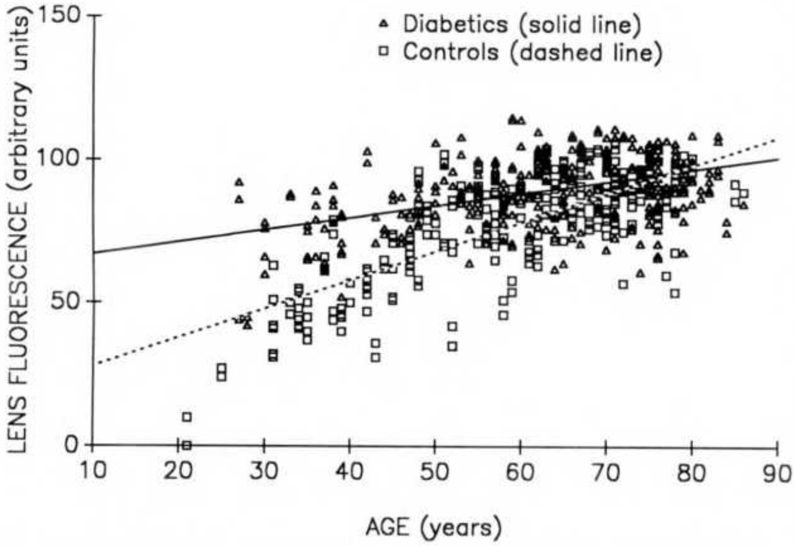

Figure 6 *Plot of lenticular autofluorescence (arbitrary units) against age (years) for eyes of 'mixed' diabetics and controls. (See text for details of these populations.) Separate linear regression lines have been shown for diabetics and controls.*

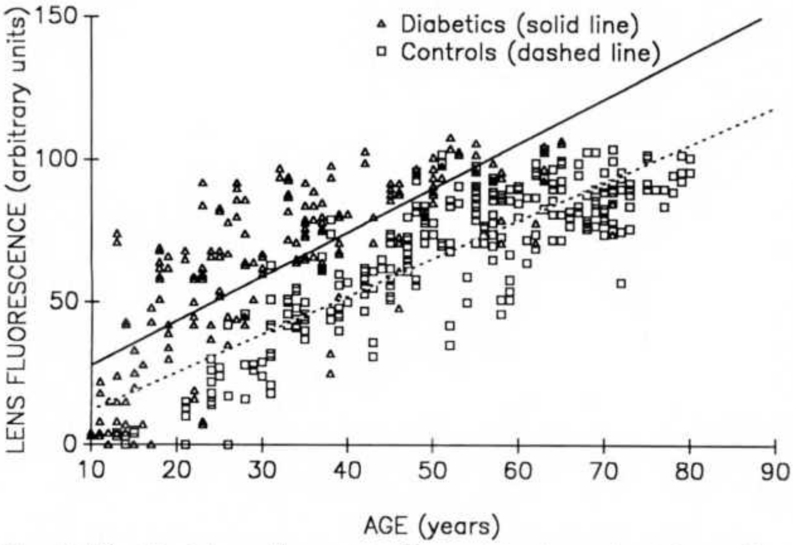

Figure 7 *Plot of lenticular autofluorescence (arbitrary units) against age (years) for eyes of early onset diabetics and controls. (See text for details of these populations.) Separate linear regression lines have been shown for diabetics and controls.*

Table 1 Summary of p values for associations between lenticular autofluorescence and patient characteristics in the community based, mixed (early and late onset) diabetic population and non-diabetic controls. A subgroup analysis of exclusively non-cataractous lenses has also been presented*

	All lenses	*Clear lenses*
Diabetics and controls (early and late onset)		
Age	$<10^{-6}$	$<10^{-6}$
Sex	0·038	0·0042
Sta	$<10^{-6}$	$<10^{-6}$
Age.sta	$<10^{-6}$	$<10^{-6}$
R for model	0·71 (*n*=294)	0·75 (*n*=224)
Diabetics (early and late onset)		
Age	$<10^{-6}$	$<10^{-6}$
Sex	NS	NS
Dur	0·013	0·0054
Type	0·0028	0·0017
Dur.type	0·023	NS
Ret	NS	NS
Dur.ret	NS	0·043
R for model	0·53 (*n*=161)	0·63 (*n*=114)
Controls		
Age	$<10^{-6}$	$<10^{-6}$
Sex	NS	NS
R for model	0·75 (*n*=133)	0·77 (*n*=110)

*Probabilities calculated in a multivariate analysis by the intraclass correlation method of Rosner (see refs 39 and 40) (Model terms were fitted in the order in which they appear in the table) Sta=diabetic or non-diabetic status; Dur=diabetic duration; Type=early or late onset type of diabetes; Ret=any diabetic retinopathy; Age.sta=interaction term between age and diabetic/non-diabetic status, Dur.type=interaction term between diabetic duration and type of diabetes; Dur ret= interaction term between diabetic duration and retinopathy; *R*=generalised correlation coefficient; *n*=number of individuals in subgroup

standardisation of the repeatability measure, the errors can be expressed as a percentage of the total dynamic range of the test within a given population of measurements (the coefficient of repeatability). By this measure there was a probability of 0·95 that any individual error would lie within the range ±13%.

STATISTICAL METHODS

A series of statistical model fitting exercises was employed. The method consisted of a multivariate extension of Rosner's intraclass correlation method.[39,40] This method takes account of the inter-eye correlation within individuals, thus avoiding exaggerated significance levels which result if eyes are treated as independent observations. This is the method of choice in the analysis of studies with a 'two eye' design such as the present work. All probability values and confidence intervals were calculated by this intraclass correlation method using the generalised linear interactive modelling (GLIM) system of the Numerical Algorithms Group (Wilkinson House, Jordan Hill Road, Oxford OX2 8DR).

Table 2 Summary of p values which illustrate differences in autofluorescence associations between late onset and early onset diabetic populations and controls. (See text for descriptions of these populations.) To facilitate comparability between the early and late onset groups, a separate analysis of exclusively clear lenses has been presented for the late onset group*

	Late onset		*Early onset clear lenses*
	All lenses	*Clear lenses*	
Diabetics and controls			
Age	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$
Sex	NS	0·031	NS
Sta	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$
Age sta	$<10^{-6}$	$<10^{-6}$	NS
R for the model	0·72 (*n*=267)	0·77 (*n*=199)	0·82 (*n*=242)
Diabetics only			
Age	0·010	0·014	$<10^{-6}$
Sex	NS	NS	0·0032
Dur	0·042	0·015	0·000011
Ret	NS	0·027	0·0064
Dur.ret	NS	NS	$<10^{-6}$
R for the model	0·32 (*n*=136)	0·43 (*n*=91)	0·88 (*n*=104)

*Probabilities calculated in a multivariate analysis by the intraclass correlation method of Rosner (see refs 39 and 40). (Model terms were fitted in the order in which they appear in the table) Sta=diabetic or non-diabetic status, Dur=diabetic duration; Ret=any diabetic retinopathy, Age sta=interaction term between age and diabetic/non-diabetic status; Dur ret=interaction term between diabetic duration and retinopathy; *R*=generalised correlation coefficient; *n*=number of individuals in subgroup.

Results

Among the mixed diabetic population and group matched controls there were 161 diabetics and 133 non-diabetics with at least one eye suitable for inclusion in the study. There were likewise 104 early onset diabetics and 138 controls (all clear lenses) in the second population. These main groups were divided into a number of subgroups, the numbers in each subgroup being indicated in the relevant summary tables (Tables 1, 2, and 4).

MIXED DIABETIC POPULATION AND CONTROLS

The first analysis (summarised in Table 1) examined the mixed diabetic population and controls. Age was clearly a very powerful determinant of lenticular fluorescence, with sex playing a relatively minor role. The variable effect of sex (greater fluorescence in males) was much reduced when the order of the terms of the model was altered such that sex was fitted after diabetic/non-diabetic status. The effect of diabetic status, after adjusting for the effects of age and sex was very powerful, and there was in addition a powerful interaction between age and diabetic status. These relationships are well demonstrated in Fig 6, where the regression line of the diabetics is on average above that of the controls (main effect) and the slope of the diabetic regression line is much less steep (interaction effect), with younger diabetics having a relatively greater excess of fluorescence than older diabetics. From the analysis of the diabetic subgroup it is apparent that after adjusting for the effect of age (sex non-significant) there were significant effects of diabetic duration and type of diabetes (early or late onset), with a moderate interaction effect between type of diabetes and diabetic duration. Among the controls, age was the only important determinant of lenticular autofluorescence. A subgroup analysis on clear lenses only gave similar results, with the duration by type interaction no longer reaching the 0·05 probability level, and a significant duration by retinopathy interaction term appearing.

LATE ONSET DIABETIC POPULATION AND CONTROLS

From the mixed diabetic population a subgroup consisting of the late onset only diabetics (and controls) was analysed. A summary of this analysis appears in Table 2. Comparing late onset diabetics with controls demonstrated powerful effects of age and diabetic status, similar to those noted above for the mixed diabetic group and controls. Within the late onset only subgroups of diabetics (Table 2, left and middle columns), the age effect was far less important than that for the mixed (Table 1) and early onset (Table 2, right column) groups, and the models for late onset diabetics fitted the data less well (see *R* values, Tables 1 and 2). After adjusting for the relatively modest effect of age in the late-onset groups, diabetic duration and retinopathy (in the clear lenses subgroup) were significant effects. There was no important interaction effect between diabetic retinopathy and duration. The powerful effect of age observed above in the combined late onset and controls groups was therefore due mainly to the effect of age amongst the controls (as documented directly in Table 1).

EARLY ONSET DIABETIC POPULATION AND CONTROLS

Analysis of the early onset only diabetics and controls (clear lenses) (Table 2, right column) demonstrated that age and diabetic/non-diabetic status were powerful determinants of lenticular autofluorescence. The interaction term between age and diabetic status however did not play a dominant role. These relationships are illustrated in Fig 7, where it is seen that the regression line of the diabetic subgroup lies well above that of the controls and further that the lines are approximately parallel (no interaction effect). The analyses on clear lenses for the early and late onset diabetic subgroups (Table 2, middle and right columns) illustrated important differences between these groups. The early onset diabetics demonstrated a powerful age effect, with sex, diabetic duration and diabetic retinopathy also having significant effects. The observed effect of sex disappeared ($p>0·05$) when this term was fitted after diabetic duration, which suggests that the apparent effect of sex may have been due to imperfect matching of diabetic duration between males and females (that is duration acting as a confounding variable). The effects of duration and retinopathy were substantially more powerful in the early onset group than in the late onset group, and in addition a powerful duration by retinopathy interaction term was confined to the early onset group. The model for the early onset group fitted the data well (clear lenses: $R=0·88$ for early onset; $R=0·43$ for late onset diabetics).

Table 3 Summary of regression slopes and effect sizes with 95% confidence intervals for diabetics (late onset and early onset) and controls. Late onset and early onset diabetic groups are contrasted, the analysis referring exclusively to non-cataractous lenses*

	Late onset	*Early onset*
Diabetics and controls		
Linear regression in groups for age and diabetic/non-diabetic status (main effects analysis)		
Age slope (effect per year)	0·9271±0·1443	1·092±0·1221
Diabetes effect (mean)	9·076±3·503	15 87±4 230
Subgroup analysis		
A. Simple linear regression for age		
Control subgroup		
Age slope	1·319±0·1253	
Diabetic subgroup		
Age slope	0·2413±0·2132	1·568±0·2483
B Multiple linear regression for age and diabetic duration (diabetic only)		
(1) Allowing age effect (slope) to vary within model		
Age slope	0·1635±0·2440	0·8274±0·4092
Duration slope	0·4565±0 3430	1·193±0·5463
(2) Age effect (slope) fixed within model to that of relevant diabetic group		
Age slope	0·2413 (fixed)	1·568 (fixed)
Duration slope	0·4224±0·3308	0·3733±0·3236
(3) Age effect (slope) fixed within model to that of non-diabetic controls		
Age slope	1·319 (fixed)	
Duration slope	−0·05113±0·4908	0·6488±0·3136

*Probabilities calculated in univeriate/multivariate analyses by the intraclass correlation method of Rosner (see refs 39 and 40). Slope=effect of regression term (age or diabetic duration) per year.

Table 4 Summary of p values for associations between lenticular autofluorescence and cataract subtypes in the community based mixed (early and late onset) diabetic population and controls*

	BR	*WS*	*SC*	*PC*
Diabetics and controls ($n=284$)	$<10^{-6}$	0·35	0·19	0·78
Mixed diabetics ($n=154$)	$<10^{-6}$	0·31	0·02	0·53
Controls ($n=130$)	0·14	0·71	0·76	0 90

*Probabilities calculated in a multivariate analysis by the intraclass correlation method of Rosner (see refs 39 and 40) The associations between cataract subtypes and lenticular autofluorescence are indicated as probability values (p values) BR=nuclear brunescence; WS=white nuclear light scatter (clinical grading), SC=central nuclear light scatter (image analysis of Scheimpflug photographs), PC=percentage cortical/subcapsular cataract (image analysis of retroillumination photographs). Confounding variables were included in the model prior to fitting the cataract feature for each group as follows: Diabetics and Controls Age, diabetic/non-diabetic status, and an interaction term between age and diabetic/non-diabetic status. Mixed diabetics Age, diabetic duration, type of diabetes (early or late onset), and an interaction term between duration and type of diabetes Controls Age

MAGNITUDE OF EFFECT FOR AGE, DIABETES, AND DIABETIC DURATION

The magnitude of some of the effects noted above are summarised in Table 3. This analysis was confined to an examination of clear lenses only which facilitates comparability between effects seen in the late onset and early onset diabetic groups. In the combined analysis of diabetics and controls (Table 3, upper section) the age slopes for the late onset and early onset groups (each combined with controls) were similar, but the overall effect of diabetes was on average a little greater in the early onset diabetics (that is main effects analysis). In the subgroup analysis the regression slope for age by simple linear regression (Table 3, item A) for the control group lay between the age slopes for the late and early onset diabetic subgroups. The magnitude of the age effect in the early onset subgroup was more than six times that of the late onset subgroup. In the multiple regression analysis where age and duration were allowed to vary independently (Table 3, item B1), the age effect per year in the early onset diabetics was five times that of the late onset group, and the effect per year of diabetic duration more than 2·5 times greater in the early onset group than in the late onset group. Because age and diabetic duration were correlated variables, the fitting of diabetic duration to this type of multiple regression model resulted in a distortion of the estimate for age. In order to avoid this two further analyses were performed in which the age effect was fixed in the model prior to the inclusion of the diabetic duration term. In the first of these last two analyses the age effect was fixed to that of the diabetic group under consideration (late or early onset), and in the second of these the age effect was fixed to that of the non-diabetic controls. With the age effect fixed to that of the relevant diabetic group (Table 3, item B2) the magnitude of the additional effect of duration after accounting for the effect of age was similar in the early and late onset diabetics. With the age effect fixed to that of the non-diabetic control group (Table 3, item B3), there was no longer any effect of diabetic duration in the late onset group. In the early onset group however a substantial duration effect remained, amounting to approximately an additional 50% per year of the 'normal' ageing effect.

ASSOCIATIONS BETWEEN CATARACT SUBTYPES AND LENTICULAR AUTOFLUORESCENCE

Associations between cataract type and lenticular fluorescence were investigated in the community based mixed diabetic population and controls. The results of these analyses are summarised in Table 4. Confounding variables were included in the models prior to fitting the cataract type under examination. In the combined analysis of diabetics and controls, nuclear brunescence (pigmentation) (BR) was powerfully associated with lenticular fluorescence. Subgroup analysis demonstrated that this association was confined to the diabetics only and further that central nuclear light scatter (SC) as measured by image analysis of Scheimpflug photographs, was also associated with fluorescence within the diabetic subgroup. The association with nuclear scatter does not appear where the measurements have been made by a simple grading method (WS) which may reflect the fact that the grading method is much less sensitive to minor changes than Scheimpflug photography combined with digital image analysis.[30 31 37] No association was found with 'percentage cataract' (PC) as measured by digital image analysis of retroillumination photographs of the lens. The 'percentage cataract' represents a composite statement about the amount of cortical and subcapsular cataract present in a lens.[37]

Discussion

This study confirms the importance of age and diabetic status in determining the visible blue/green (excitation around 420 to 430 nm, emission around 520 nm) autofluorescence of the human lens.[7–11 18] Diabetic duration has been confirmed as an important determinant of blue/green autofluorescence.[11 18] The present work provides new information regarding the effect on lenticular autofluorescence of diabetes and diabetic duration in separate groups of early onset and late onset diabetics and controls. The 'clear lens' analyses presented highlight differences in the impact of diabetic duration on autofluorescence in early and late onset diabetes. In previous studies employing multiple linear regression no analysis has been presented in which the age effect of non-diabetics was imposed on a diabetic group to assess the independent effect of diabetic duration over and above the 'normal' ageing effect.[11 18] Here various methods of estimating the additional effect of diabetic duration after accounting for the effect of age have been presented and these illustrate the effect per year of diabetic duration and demonstrate differences between the early onset and late onset diabetics. The existence of diabetic retinopathy has been found to be of striking importance in early onset diabetics, while the effect of sex was variable. The reasons for the differences between the early and late onset diabetics are not clear and require explanation. Information on metabolic control was not available in this study, so it is not possible to comment upon the published finding that poor metabolic control is associated with increased blue/green autofluorescence.[18]

A powerful association between nuclear brunescence (pigmentation) and autofluorescence has been demonstrated, this effect being confined to the diabetic subgroup. Previous in vitro work has demonstrated increased lenticular fluorescence in the 520 nm emission region in brown nuclear cataracts but not in cortical cataracts, suggesting an association between the existence of the brunescent pigment and the blue/green fluorogen.[8 17] The present in vivo study confirms this association and, importantly, demonstrates that this effect was dominant among the diabetics in the population studied. A weaker association between autofluorescence and increased central nuclear light scatter as measured by image analysis of Scheimpflug photographs has also been identified in the diabetic subgroup.

Non-enzymatic glycosylation of lens proteins is known to occur both in diabetics and in normal individuals. The process increases with age and is increased in diabetes.[24 27 41] Glycosylation occurs at free amino groups with the formation of stable products ('browning'), and may be of importance in the normal processes of protein ageing.[21 22 42] Conformational changes following glycosylation result in unfolding of crystallins, allowing the formation of light scattering macromolecular complexes by oxidation of exposed thiol groups.[25 43 44] In cataracts from human diabetics specific changes of lens proteins,[45] and excess glycosylation products have been found.[41 46] 'Browned' glycosylation products of polypeptides have been shown to exhibit fluorescence at around 370 nm excitation and 440 nm emission.[26 27] Brown nuclear cataracts exhibit fluorescence at these wavelengths[6 8 12–15] but lenses are also known to fluoresce at other wavelengths,[7–11] with the most intense fluorescence in brunescent cataractous lenses in the 520 nm emission range[8 17] (as studied here). Previous workers have stressed the link between the pigment of nuclear brunescence and the UV/blue fluorogen (emission 440 nm).[6 12 13 21–23 26] Photochemical changes to tryptophan within lens proteins have been suggested as a possible mechanism of production of UV/blue 'fluorescent chromophores'.[8 47] UV/blue fluorescence of non-enzymatic glycosylation products of 'browned' proteins have however been demonstrated suggesting that protein derived 'fluorescent chromophors' in the lens nucleus are products of non-enzymatic glycosylation.[21 22 26]

Non-enzymatic fructation of proteins with the production of protein bound UV/blue fluorescence has been demonstrated, the generation of the fluorescent products from fructation being 10 times faster than from glycosylation.[48] Polyol degradation products could account for increased fructose in young diabetic lenses, although the activity of aldose reductase in lenses of adult diabetics is extremely low.[17]

The longer wavelength blue/green fluorogen may be derived from the shorter wavelength UV/blue fluorogen,[8 19] in which case brunescence and the two fluorogens could share a common mechanism of production. It is possible that the pigmented species in nuclear cataract are related to the fluorogen responsible for the blue/green fluorescence seen in diabetic lenses. In the present work, after accounting for confounding effects, there is a powerful association between lenticular fluorescence and brunescence (and to a lesser extent nuclear light scatter) in the diabetic subgroup, with fluorescence and brunescence each increasing with age and diabetic duration. Clearly other mechanisms could be active but non-enzymatic glycation must remain a strong contender as a possible mechanism of production of the fluorogen with emission around 520 nm, which itself may be linked to the pigment of nuclear brunescence.

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Modelling of changes in the corneal endothelium after cataract surgery and penetrating keratoplasty

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Abstract

Long term changes in endothelial cell density were monitored in three groups of patients after surgery. One group underwent uncomplicated cataract surgery, one group complicated cataract surgery which eventually progressed to corneal decompensation, and one group penetrating keratoplasty. A mathematical model is presented which describes endothelial cell loss after surgery as an exponential decay process towards an asymptote with constant rate of cell loss over time. When fitted to the data from the three groups there is excellent agreement in each case. Discriminant analysis techniques were applied to model predictions to assess the likelihood of late corneal decompensation after surgery. From measurements of endothelial cell density before and after surgery we were able to correctly assign patients undergoing cataract surgery to decompensation or non-decompensation groups in 85·7% and 92·7% of cases respectively.

The changes which occur in the corneal endothelium after cataract surgery and penetrating keratoplasty are well documented, both in terms of endothelial cell density and morphology.[1-4] However little attempt has been made to assess whether these changes conform to a mathematical model and are therefore predictable.[3] We have previously described such a model[5] in a preliminary report. We have now extended these observations to an increased number of patients after cataract extraction and also have examined patients undergoing penetrating keratoplasty to see if they too conform to this type of mathematical model.

Methods

Three groups of patients were studied. The first two came from a randomised controlled trial of cataract surgery,[6] which was commenced in 1981, in which patients were followed for a minimum of 5 years with no loss to follow up except through death. In this trial there were 117 patients whose surgery was completely uneventful both per- and postoperatively (group 1). Some of these patients had intracapsular cataract extraction, either with or without an iris clip intraocular lens and some had extracapsular extraction with a Binkhorst 2 loop iridocapsular lens. Another group of 14 patients were identified who had complications at surgery and ultimately progressed to corneal decompensation (group 2). These patients had one or other of the intraocular lenses. The third group consisted of 25 patients with keratoconus who underwent penetrating keratoplasty at Moorfields and who have been followed with serial endothelial cell counts after surgery (group 3).

The patients undergoing cataract surgery had endothelial cell photographs using non-contact specular microscopy, preoperatively, at 1 month, 6 months, and then yearly after surgery. Cell density was derived by counting cells within a grid of known size and masking procedures were used. The method has been described[7] and its precision estimated.[8]

The patients undergoing penetrating keratoplasty were photographed by contact specular microscopy and density was again derived by grid counting. The first cell count was performed as soon as possible after surgery, usually within the first week, and then after 1, 3, 6, and 9 months, as well as annually thereafter.

STATISTICAL METHODS

Using the endothelial cell counts for those patients who underwent uneventful surgery (group 1), the following analysis was undertaken. The mean cell count was calculated at each time point and an empirical curve of exponential type was fitted to these values. As we found in our previous work[5] that an improved fit was obtained if an asymptote was included, this type of model was again used here to represent the number of cells which the decay process seems to be approaching. Using the best fitting empirical model allowed the prediction of cell loss directly and also provided a means of smoothing individual counts (which may be subject to sampling error) so that classification techniques could be applied to predict the long term outcome for patients following surgery.

For an individual patient, the recorded cell count values y_t at time t (in months), seem to follow the model:

$$y_t = a + b.r^t \pm e_t$$

where e_t is the random error in the count (due to sampling error, difficulties in visualisation of cells etc), a is the asymptotic cell count, towards which the count appears to be reducing, b is the preoperative cell count in excess of a, and r is the rate of reduction in the count per month. The model treats endothelial cell loss after surgery as an exponential decay process with a steady rate of loss over time. This type of model applies in many biological situations, for example cell loss after damage by irradiation.

Using this model and measured endothelial cell counts a cell loss curve was generated for patients in the other groups. Discriminant analysis may then be performed to see whether the curve for that patient lies closer to the curve of the group of patients who decompensated

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after cataract surgery or the curve of those that did not. It thus affords a means of predicting whether decompensation will occur. The accuracy of this technique was assessed by looking at the patients in our study who underwent cataract surgery and in whom it was known whether decompensation occurred to see how many of them were ascribed to the correct group. It was also possible to establish which of the postoperative counts in conjunction with the preoperative count gave the best prediction of the eventual outcome for a new patient.

The performance of linear and quadratic discriminant functions (LDA and QDA) were compared and the cross-validation technique was used to reduce the bias in the estimated misclassification rates for these methods. These discriminant techniques are discussed by Friedman[9] and the determination of misclassification rates used here is described by Lachenbruch.[10]

For comparison with the above multivariate discriminant methods, a simpler graphical technique was also examined based upon the position of the plotted counts for an individual to be classified in relation to the mean curves for the groups. The patient was then allocated to the group whose curve was closest to the plotted counts for that patient. Unfortunately the results of this technique were consistently less good than those found using any of the discriminant methods. This approach was therefore not pursued.

Results

The longitudinal changes in endothelial cell density in the three groups of patients are shown in Tables 1 and 2. The 2 year cell density value for group 3 may be erroneously low due to the small number of values at this time point. When these changes are plotted against time (Figs 1 to 3) group 2 clearly follows an exponential type curve and the other groups also follow a similar form of curve.

Simultaneous fitting of the curves to the groups produces a common asymptote value of 377·6 (SD 190·1). The rates of cell depletion differed for the three groups as shown by the r values. For those patients developing corneal decompensation this rate was 0·949 (SD 0·016), for those in the corneal graft group it was lower at 0·971 (SD 0·006), and for the uncomplicated cataract extraction group it was lowest at 0·995 (SD 0·002).

Table 1 Endothelial cell density after uncomplicated and complicated cataract surgery

	Group 1 (uncomplicated) (cells/mm^2)	*Group 2 (complicated) (cells/mm^2)*
Pre-op	2670 SD 436 n=117	2424 SD 482 n=14
1 month	2378 SD 365 n=101	1986 SD 627 n=9
6 months	2351 SD 313 n=112	1674 SD 585 n=14
1 year	2244 SD 435 n=103	1206 SD 502 n=14
2 years	2086 SD 648 n=97	853 SD 452 n=14
3 years	2024 SD 685 n=85	645 SD 219 n=11
4 years	1916 SD 708 n=79	586 SD 233 n=8
5 years	1747 SD 830 n=10	

Table 2 Endothelial cell density after penetrating keratoplasty

	Group 3 (cells/mm^2)
Early post-op	2548 SD 264 n=24
1 month	2202 SD 295 n=21
3 months	2114 SD 374 n=22
6 months	2065 SD 375 n=23
9 months	1938 SD 385 n=24
1 year	1896 SD 403 n=21
18 months	1775 SD 481 n=10
2 years	1025 SD 231 n=3

In those patients who progressed to corneal decompensation (group 2) this occurred at a mean time after surgery of 44·6 (SD 4·1) months. The measured endothelial cell density at the time of decompensation was 495 (SD 34) cells per mm^2. This is in agreement with other studies[11 12] and with predictions made on the basis of endothelial physiology and in particular pump site density.

Standard survival data analysis when applied to the model curve for group 2 produced a mean time to decompensation of 50·1 (SD 2·4) months and predicted that cell density at decompensation would be 542 (SD 36) cells per mm^2 which are close to the means of the observed values.

If the model is applied to group 1, which underwent uncomplicated surgery, it predicts that these eyes too will eventually decompensate at some 477 months after surgery. This form of prediction cannot be applied accurately to the corneal graft group since it does not take into account movement of cells between donor and host tissue. When the observed longitudinal changes in endothelial cell density are compared with predicted values obtained using our model there is excellent agreement. Fig 4 shows the measured values of cell density after uncomplicated cataract extraction as open symbols while

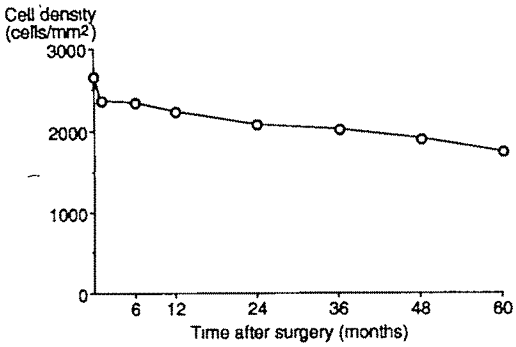

Figure 1 Pattern of change in endothelial cell density after uncomplicated cataract extraction.

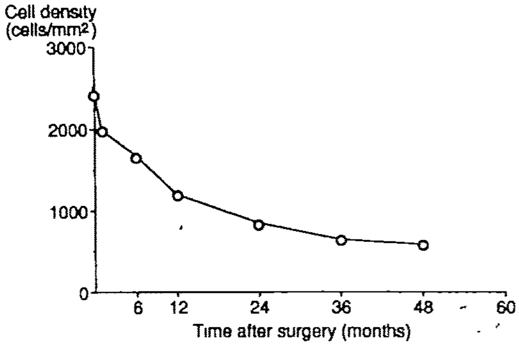

Figure 2 Pattern of change in endothelial cell density after complicated cataract extraction progressing to corneal decompensation

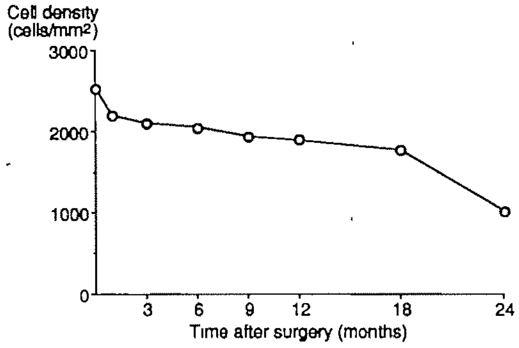

Figure 3 Pattern of change in endothelial cell density after uncomplicated penetrating keratoplasty for keratoconus.

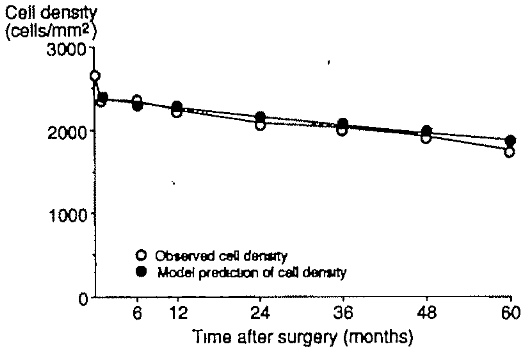

Figure 4 Comparison of model predictions and observed endothelial cell counts in uncomplicated cataract extraction.

those values predicted by the model at each time point are shown as filled symbols.

Similarly after complicated extraction progressing to corneal decompensation (Fig 5) the model predictions shown are once again very close to the values actually observed.

This close agreement also applies for the corneal graft group (Fig 6) although there may be some deviation later due to migration of host cells. Furthermore the 2 year value observed may be artificially low due to the small number of patients recorded so far at this time point.

Using the discriminant analysis techniques described the 14 patients who decompensated were examined. For this the preoperative cell count was used in conjunction with either the 1 year or 2 year cell counts or both. As shown in Table 3 the method correctly predicts that decompensation would occur in 85·7% of these patients if either or both of these time points was used.

The same procedure was then applied to patients who did not decompensate after surgery (group 1) and who had endothelial cell counts available at all time points (Table 4). Eighty seven per cent were correctly predicted not to decompensate on the basis of the 1 year count in conjunction with the preoperative count, 90·0% if the 2 year count was used, and if both values were used this rose to 92·7% in the linear analysis.

The close agreement between the linear and quadratic methods suggests that little further improvement would be expected using Friedman's regularised discriminant analysis. Although this method was not pursued in this situation, it may well be appropriate where smaller samples from more heterogeneous populations are involved.

Discussion

The values observed for decline in endothelial cell density in the three groups (Tables 1 and 2) are of similar orders of magnitude to other studies in the literature and, in the case of the first two groups, have already been fully reported.[1] However in this instance it was the profile of longitudinal cell loss with which we were concerned rather than the absolute values.

As in our preliminary report[5] excellent agreement was found between the observed values of longitudinal endothelial cell density and those predicted by the model after both uncomplicated and complicated cataract extraction. With greater numbers of patients included the fit is improved.

This is the first time that we have examined patients after penetrating keratoplasty and it was interesting to find that there was again close agreement between observed and predicted values. We are aware of only one other attempt to model changes in the corneal endothelium after corneal grafting.[3] It appears that the fit between model and actual values is less good at later time points than after cataract extraction. This is likely to reflect remodelling with movement of cells between host and donor tissue which is not presently taken into account in model predictions.

The prediction obtained, using the model, that late corneal decompensation is likely to occur eventually after even uncomplicated cataract surgery some 477 months later is inter-

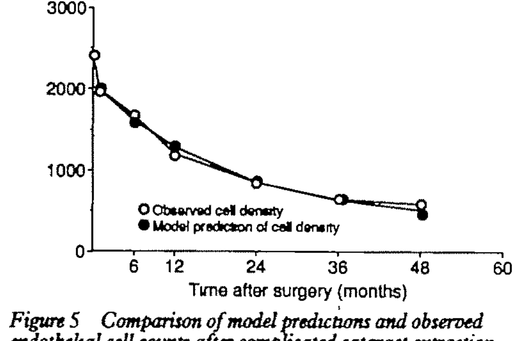

Figure 5 Comparison of model predictions and observed endothelial cell counts after complicated cataract extraction progressing to corneal decompensation.

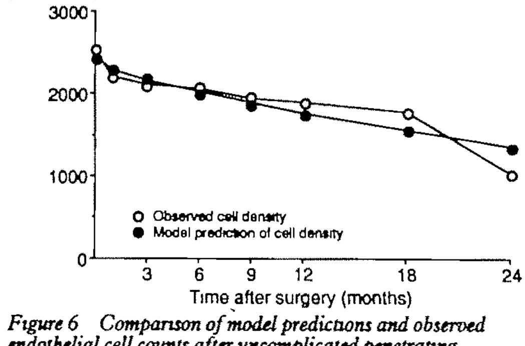

Figure 6 Comparison of model predictions and observed endothelial cell counts after uncomplicated penetrating keratoplasty for keratoconus.

Table 3 Cross-validated error rates for the prediction of outcome using two methods of discriminant analysis for the corneal decompensation group

	Linear analysis		*Quadratic analysis*	
	Correctly classified	*Incorrectly classified*	*Correctly classified*	*Incorrectly classified*
Pre-op+				
1 year	12 (85·7%)	2	12	2
2 years	12	2	12	2
Both years	12	2	12	2

Table 4 Cross-validated error rates for the prediction of outcome using discriminant analysis for the uncomplicated cataract surgery group

	Linear analysis		*Quadratic analysis*	
	Correctly classified	*Incorrectly classified*	*Correctly classified*	*Incorrectly classified*
Pre-op+				
1 year	83 (86·5%)	13	84 (87·5%)	12
2 years	86 (89 6%)	10	86 (89·6%)	10
Both years	89 (92·7%)	7	86 (89 6%)	10

esting and of some concern in view of the early age at which some patients now undergo cataract extraction with or without intraocular lens implantation. It relates to the fact that, in this as in other studies, although the annual cell loss after cataract surgery levels off after approximately 4 years it continues to be slightly greater than that for an unoperated eye, in this case 0·7% versus a typical value of 0·5%.[8] It is of course possible that eventually the cell loss will normalise absolutely such that this prediction would become incorrect, but in view of the length of follow up here and the increasing frequency of late corneal decompensation observed clinically we suspect that this may not be the case and therefore our prediction should be considered in discussing cataract surgery with young patients.

Discriminant analysis may be used in conjunction with model predictions to assess the likelihood of late corneal decompensation after surgery. When used here on those patients undergoing cataract surgery it correctly assigned 85·7% of the eyes with bullous keratopathy to this fate using the preoperative cell counts with either the 1 year postoperative count, the 2 year count or both (Table 3). Those eyes which did not decompensate were correctly classified in 86·5% of cases using the preoperative and 1 year count; in 89·6% of cases using the preoperative and 2 year count; and 92·7% of cases if both these postoperative values were used by a linear discriminant function (Table 4). The corresponding values were very similar when quadratic discriminant analysis was used.

Thus using our model in conjunction with discriminant analysis those eyes which are likely to progress to corneal decompensation can be predicted with a high degree of accuracy from only two endothelial cell counts.

We foresee a number of potential clinical applications for this type of model. As shown it may be used after surgery to predict the likelihood of progression to corneal decompensation and its time course.

At the present time there are a number of clinical situations where it would be of value to be able to assess the likelihood of development of corneal decompensation, for example when considering implanting an intraocular lens in the second eye of a young patient or when performing cataract surgery on an eye with a corneal graft. It is hoped that model predictions will allow this risk to be assessed more accurately and so facilitate appropriate management.

Model predictions may also be used to give more rapid evaluation of the effects of new techniques or products used in surgery on the cornea or of different methods of storage of graft material.

In conclusion our work thus far has shown that the changes which occur in the corneal endothelium after surgery may be accurately modelled and so are predictable and we believe that this may have a number of clinical applications.

We would like to thank Mr R J Buckley for kindly allowing us to use endothelial cell counts on patients under his care after penetrating keratoplasty We would like to thank Don Barbour for photographic assistance, Anne Ambrose for cell counting and Jane Fallows for graphics.

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Survey of the contamination of eyedrops of hospital inpatients and recommendations for the changing of current practice in eyedrop dispensing

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Abstract

Topical ophthalmic medications used on the ward and from the outpatient area have been taken and cultured for potential bacterial contamination in the laboratory. We examined 143 bottles used by patients who had had routine cataract surgery and trabeculectomy. We also examined for bacterial contamination 216 bottles of eyedrops used in the outpatient area of the hospital. No contamination was found in the postoperative eyedrops, but five bottles were contaminated from the outpatient area (2·3%). The bacterial growth from outpatient drops was of the same order of magnitude as in previous studies. The practice in the UK for postoperative eyedrops to be discarded and fresh, separate bottles to take home is discussed. We recommend that this practice be changed so that the postoperative drops used for 72 hours or less are taken home.

The duration of inpatient stay has decreased steadily in the UK with decreasing time of postoperative stay[1 2] (Fig 1). Many patients are now discharged the evening following surgery or the next day. We wished to assess whether short-stay patients having routine surgery who used postoperative eyedrops had contamination of these drops on leaving hospital. Since in a pilot study we had failed to detect contamination in these bottles, we attempted to assess the efficacy of the bacterial assay by culturing multiuse bottles used in the outpatient area of Moorfields Eye Hospital.

Previous studies have been performed on the contamination of ocular medications, and variable growth of bacterial contaminants has been obtained.[3–11] One study in an ophthalmic outpatient clinic found tear contamination of eye-dropper bottles,[12] and a number of studies have commented on the inhibition of growth of bacteria by preservatives. The survival of organisms has been found in the bottle dead space and cap.[13–15]

There has been improvement in the efficacy of preservatives used in eyedrop preparations,[13 14 16–18] and modern multidrop bottles may be expected to have a very low level of contamination with viable bacterial organisms. To test the efficacy of antimicrobial presevative the British Pharmacopoeia Commission set up a working party in 1988 to study multidose ophthalmic products. Eyedrops were selected owing to their differing preservatives, their initial sterility, and their frequency of use.[19] Four different preparations were studied, and contamination was found in 5% of 604 samples. Only low levels of contamination were generally found, with higher levels restricted to a few samples containing coagulase-negative staphylococci.

In the United Kingdom it is policy that unidrop dispensers are used for external disease clinic outpatients and all patients for a casualty department owing to the fear of infection.[20] Multidrop bottles should not be used in these areas. Currently Moorfields Eye Hospital use multidrop bottles for outpatient clinics and wards. Unidrop dispensers are used for the casualty department and external eye disease patients.

Material and methods

SPECIMENS COLLECTED

One hundred and forty three multidrop bottles from postoperative, routine, non-infected, cataract and trabeculectomy patients were assessed. The eyedrops were prepared in Moorfields Eye Hospital Pharmacy Department and issued for use in amber glass bottles. Screw

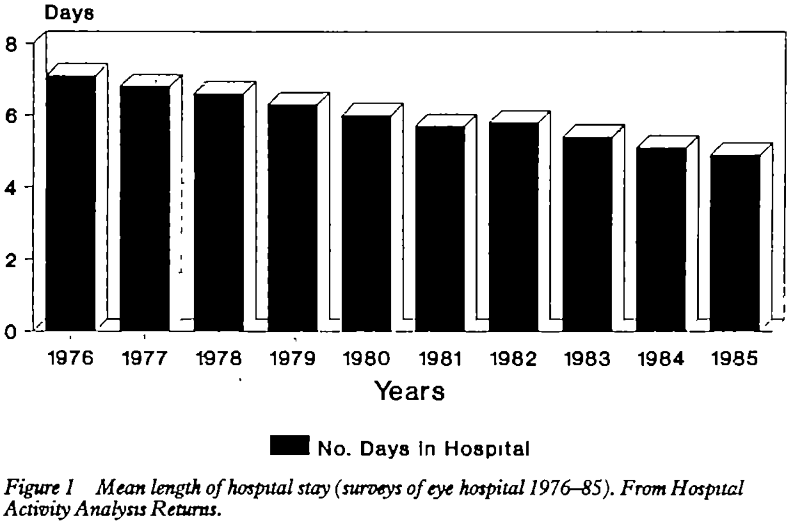

Figure 1 Mean length of hospital stay (surveys of eye hospital 1976–85). From Hospital Activity Analysis Returns.

Table 1 Eyedrops from postoperative routine patients

Dexamethasone 0·1%	(0·005% Thiomersal)	80
Cyclopentolate 1%	(0·01% Benzalkonium chloride)	38
Prednisolone 1%	(0·01% Benzalkonium chloride)	16
Phenylephrine 10%	(0·01% Benzalkonium chloride)	2
Prednisolone 0·3%	(0·01% Benzalkonium chloride)	2
Timolol 0·25%	(0·01% Benzalkonium chloride)	2
Cyclopentolate 1%	(Without preservative)	1
Adrenaline 0·1%	(Without preservative)	1
Atropine 1%	(0·01% Benzalkonium chloride)	1
Total		143
Number contaminated		0

caps are fitted with integral glass droppers. These bottles were used for one or two days by a single patient and then discarded on discharge of the patient from hospital. In each case the patient subsequently received identical multidrop bottles to take home. No multidrop bottles were examined that had been used for more than 72 hours on the ward. After collection, the contents of the bottles were immediately taken for bacterial culture.

We also examined 216 bottles from outpatient areas of the hospital in an identical way. These bottles have been used for eyedrop application to different patients during one clinic session before being discarded. Bottles were collected for bacterial culture at the end of the clinic session.

BACTERIAL CULTURE

Approximately 0·5 ml of each solution was cultured in 20 ml of thioglycollate (Brewer) broth (Fig 2). This not only acts as an enrichment medium, but helps to dilute out any antibacterial effect of the preservative in the dropper bottles. After 24 hours incubation in CO_2 at 37°C the broth was examined for bacterial growth. Each broth was then subcultured on blood agar in aerobic conditions and again incubated for the same period. These plates were then examined for any growth, and any pathogens were identified. All thioglycollate broth cultures were subsequently examined at 10 days. The anaerobic bottle with thioglycollate broth supported growth of *Pseudomonas* as well as sporing and non-sporing anaerobes. The combination of Brewer broth and the agar plates allowed a very wide spectrum of organisms to be cultured.

Results

Dropper bottles used by 143 postoperative patients were cultured and none were found to be contaminated (Table 1). Two hundred and sixteen bottles used in the out-patient area were taken, and five bottles grew organisms (Table 2). A light growth of *Staphylococcus epidermidis* grew from one bottle of cyclopentolate 1% (0·01% benzalkonium chloride preservative), and a mixed growth of *Staphylococcus aureus* and *Staph epidermidis* was obtained from four bottles of phenylephrine 10% (0·01% benzalkonium chloride preservative).

For the outpatient multidrop bottles 149 used benzalkonium chloride as preservative. All five contaminated bottles had benzalkonium chloride as preservative, giving a 3·4% contamination rate for this preservative. The overall contamination rate was 2·3% for all out-patient bottles.

Discussion

OUTPATIENT AND MULTIDROPS

The 2·3% contamination rate of the outpatient dropper bottles is consistent with the findings in previous studies.[3-11,19] The differing incidences of contamination recorded in other studies may be partly due to differences in procedures and microbiological methods rather than true differences in incidence.[19] Whether there is a difference in preservative efficacy was not addressed in this study, but it is interesting that the five contaminated bottles all used benzalkonium chloride as the preservative. The study of the British Pharmacopoeia Commission found that samples with relatively high bacterial counts were those from bottles preserved with thiomersal,[19] and the continued use of thiomersal in eyedrops has been questioned.[3] We have not found contamination in thiomersal preserved bottles, but in our study only 13 bottles using this preservative were collected from the outpatient clinics. Whichever preservative is used, multidrop dropper bottles are known to be a vector for potential contamination from one patient to another[12] and care should be exercised in the drop application technique.

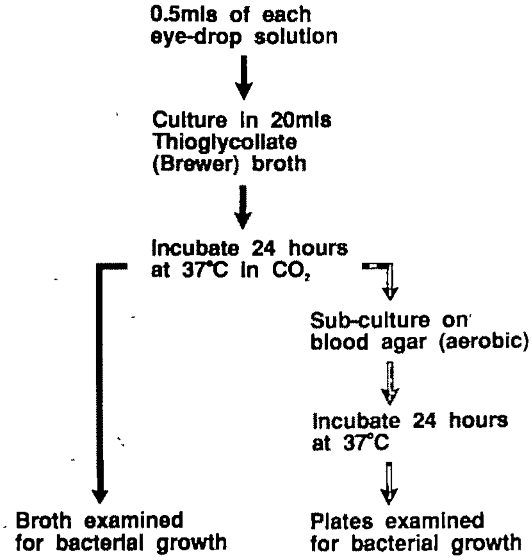
0.5mls of each eye-drop solution
Culture in 20mls Thioglycollate (Brewer) broth
Incubate 24 hours at 37°C in CO_2
Sub-culture on blood agar (aerobic)
Incubate 24 hours at 37°C
Broth examined for bacterial growth
Plates examined for bacterial growth

Figure 2 Method for culture of eyedrops.

The use of multidrop bottles in outpatient areas where a bottle is used for different patients is potentially a source of interpatient contamination. Ideally only unidrop disposable eyedrop containers would be used, but they can cost more than multidrop bottles. For any patient that might be infected or have external eye disease a unidrop dispenser should be used. Alternatively the multidrop bottle could be discarded after use with an infected or potentially infected patient. We have not recorded if some of the bottles in this study were discarded by clinic staff after such use.

Table 2 Eyedrops from the outpatient clinic area

Cyclopentolate 1%	(0·01% Benzalkonium chloride)	46
Phenylephrine 10%	(0·01% Benzalkonium chloride)	42
Benoxinate 0·3% and fluorescein 0·125%	(0·004% Phenylmercuric nitrate)	28
Pilocarpine 2%	(0·01% Benzalkonium chloride)	21
Tropicamide 1%	(0·01% Benzalkonium chloride)	19
Amethocaine 1%	(0·002% Phenylmercuric nitrate)	15
Tropicamide 1%	(0·01% Benzalkonium chloride)	15
Isotonic saline	(0·005% Thiomersal)	13
Benoxinate 0·4%	(0·01% Chlorhexidine acetate)	10
Eserine 0·5%	(0·01% Benzalkonium chloride)	2
Atropine 1%	(0·01% Benzalkonium chloride)	2
Phenylephrine 5%	(0·01% Benzalkonium chloride)	2
Cocaine 4%	(0·002% Phenylmercuric nitrate)	1
Total		216
Number contaminated		5

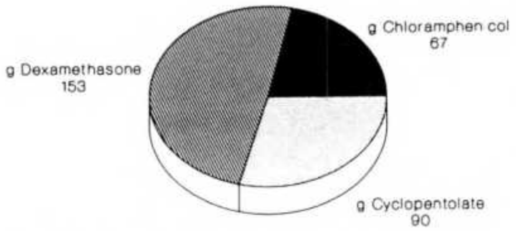

Figure 3 Cost of postoperative eyedrops (pence). From British National Formulary, *1989.*

INPATIENT DROPS

For inpatient use the current practice in the UK is for each patient to have a set of postoperative medications while in hospital and a duplicate set to take home.[19] This practice has not changed since the time that patients entering an ophthalmic ward and receiving surgery routinely stayed for many days postoperatively. Almost always those drugs to take home are identical to those prescribed for use on the ward. Modern practice has resulted in shorter inpatient stay, and an increasing proportion of patients undergo ophthalmic surgery as day cases.

In the interests of infection control each inpatient has their own set of drops while on the ward. Usually this comprises a topical steroid, an antibiotic, and in some cases a dilating drop. At present the postoperative stay in hospital is routinely one or two days,[1 2] and a bottle of drops lasts up to one month. On the ward, often, only one or two drops are used before the bottle is then discarded as the patient is discharged.

We did not find any bacterial contamination of inpatient postoperative eyedrops for cataract and trabeculectomy patients. For these routine, non-infected, short-stay patients we propose that, to save costs and to increase efficiency, medical staff should prescribe postoperative drops at the postoperative ward round, and patients should use them both on the ward and to take home, provided the bottle has not been open for longer than 72 hours. Since this study has reviewed postoperative contamination only for short-stay patients, we cannot exclude contamination of bottles opened for longer periods of time.

Not replacing the postoperative eyedrops used on the ward and allowing patients to take the same bottles home would reduce postoperative drug costs by up to 50% (Fig 3). There would also be a reduction of work load for ward, medical, and pharmacy staff. Mistakes and omissions should also decrease. Patients on being discharged do not have to wait for their drops to arrive from the hospital pharmacy, and can leave hospital much quicker, so vacating a bed sooner.

On admission to hospital, instruction is given by nursing staff in technique of instillation. By dispensing the same drops on the ward as will be used at home, the time in hospital allows patients to practice instilling the same drops. Patients would not become confused by a different brand of eyedrop being dispensed just prior to leaving hospital.

We acknowledge with thanks the help of Mr V Andrews, principal pharmacist, Moorfields Eye Hospital, and Miss J Bloom, staff pharmacist, Moorfields Eye Hospital.

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Spontaneous congenital non-pigmented epithelial cysts of the iris stroma

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Abstract

Histopathological and immunohistochemical findings in 11 patients with spontaneous congenital non-pigmented epithelial cysts of the iris stroma were studied. The cysts were lined by stratified squamous to unilayered cuboidal non-pigmented epithelium. Goblet cells were present in nine cysts, indicating a similarity to conjunctival epithelium. The demonstration of higher-molecular-weight keratins and absence of S-100 protein, by monoclonal and polyclonal antibodies, argues for surface ectodermal rather than neuroectodermal origin of the cysts. Theories of embryogenesis have been conflicting, but our results support the theory that they arise from surface ectoderm, displaced probably at the time of lens vesicle formation. The finding of normally sited subepithelial S-100 positive melanocytes may suggest that ectopic conjunctival epithelium can induce normal patterns of migration of neural crest cells.

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Spontaneous congenital non-pigmented epithelial cysts of the iris stroma are uncommon unilateral lesions, usually presenting in the first few months of life. They appear as thin walled vesicles on the anterior surface of the iris, projecting into the anterior chamber. Clinically and histologically it is very difficult to distinguish spontaneous stromal cysts from acquired (for example, post-traumatic) stromal cysts, but the latter usually give rise to more complications, such as secondary glaucoma, corneal oedema, and iridocyclitis.[1]

Whereas acquired stromal cysts are known to arise from implanted surface epithelium after penetrating ocular trauma or surgery,[2] the aetiology of spontaneous stromal cysts has been a matter of longstanding controversy, and neuroectodermal,[3-11] surface ectodermal,[12-19] and mesodermal[20-22] origins have been suggested in different reports.

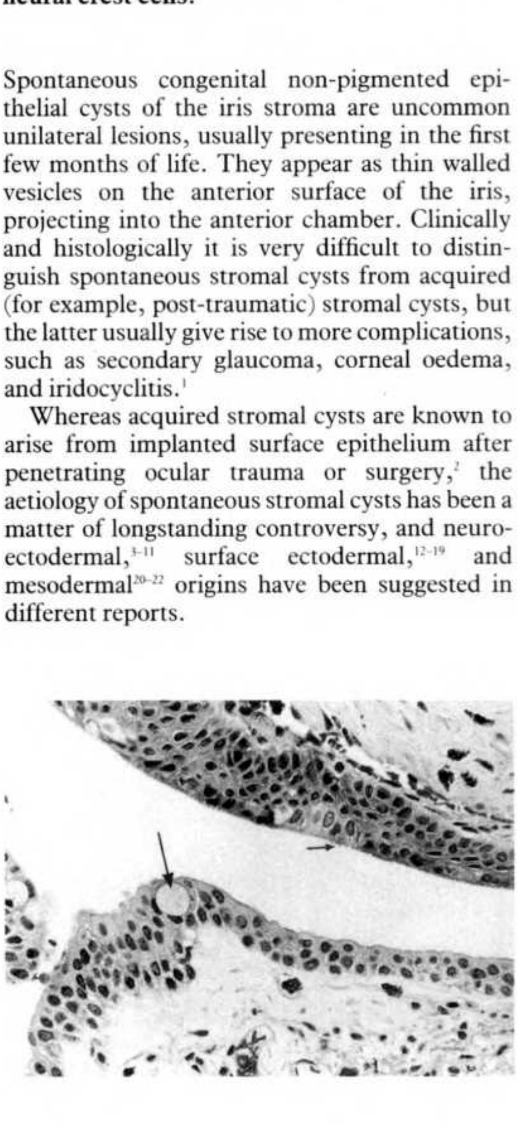


Figure 1 The epithelium which lines the lumen of this congenital iris cyst is composed of a layer of stratified cuboidal cells with prominent goblet cells (large arrow), and very occasional oligocilia (small arrow). (Haematoxylin and eosin, ×225.)

We examined the histopathological and immunohistochemical features of spontaneous non-pigmented epithelial cysts of the iris stroma in a series of 11 patients. On the basis of these observations we discuss the most plausible histopathogenetic theory for this iris lesion.

Case report

In September 1986 a girl aged 10 months, was seen at the Hospital for Sick Children, London. She had been born at term following a normal pregnancy and delivery. Her general health and development had also been normal. The family history was normal. When she was 2 months old her parents noticed a 'freckle' on the iris of the left eye. On examination a brownish, semitranslucent cystic lesion was seen in the iris stroma, replacing it and distorting the pupil. It was located inferiorly and involved the full iris thickness, bulging forward into the anterior chamber, and touching the corneal endothelium. Iris tissue behind the cyst was present but greatly thinned.

A CT scan and ultrasound examination showed no other abnormality. On 22 October 1986 the cyst was aspirated. Using healonid we stripped the cyst from the endothelium. Only partial removal and marsupialisation were possible, because the posterior leaf of the cyst formed the anterior leaf of the iris stroma.

This procedure failed to prevent recurrence, and shortly afterwards the cyst reformed. On 19 November 1986 a scleral and corneal flap was made inferiorly and a large sector iridectomy was carried out, with complete removal of the cyst. Postoperatively the eye settled well and no complications were seen.

The aspirate from the cyst showed clumps of epithelial cells and neutrophils. The iris cyst was lined by a layer of stratified cuboidal cells with prominent goblet cells, and very occasional oligocilia, on top of a layer of attenuated iris stroma (Fig 1).

Materials and methods

Pathological records, dating from 1952 through 1990 and kept in the Department of Pathology, Institute of Ophthalmology, were reviewed for patients with spontaneous congenital cysts of the iris stroma. Clinical notes, kept in Moorfield Eye Hospital, were analysed in addition to the pathology records. When the clinical notes were missing, the referring ophthalmologist was contacted for further information. For each patient we recorded as completely as possible the following data: date of birth, age at treatment, sex, laterality, history of trauma (including intrauterine trauma), associated ocular findings (decrease of visual acuity, inflammation, glaucoma, corneal oedema, cataract), referring diagnosis, clinical course, type of treatment, and complications. Patients with a documented history of (intrauterine) trauma or perforating injuries were excluded from this study.

Sections stained with haematoxylin and eosin and periodic acid Schiff were reviewed to verify the diagnosis of congenital cyst of the iris stroma. All selected specimens were subsequently stained with antibodies to S-100 antigen (DAKO) and cytokeratins (CAM 5·2 (mouse IgG2a, Becton and Dickinson) and wide spectrum screening rabbit polyclonal antikeratins (A575 and Z622, DAKO)) by means of a standard peroxidase-antiperoxidase technique, except when celloidin sections only were available.

The type of epithelium was recorded, as was the presence of goblet cells, keratinisation, hypo- or hyperplasia of the iris stroma, the presence of a basal lamina, cataractous lens remnants, and the results of staining patterns with the panel of antibodies.

Results

Records of 13 patients with a diagnosis of iris stromal cyst were reviewed. Two patients were excluded from this study: one patient has a history of penetrating ocular trauma, while the other had an iris cyst originating from the iris pigment epithelium. In the selected group of patients eight were male and three were female. Eight patients had presented with an iris stromal cyst at birth or early childhood, while in three patients the cyst had become visible only in adulthood. In eight patients the right eye was involved, in three the left. No bilateral disease was noted. In 10 patients the referring diagnosis was congenital cyst of the iris (stroma), and one patient (Table 1, no. 8) was referred with a diagnosis of buphthalmic eye with congenital abnormality.

In none of the selected patients was there a documented history of (intrauterine) trauma or surgery. In two patients there was marked inflammation of the iris cyst and the surrounding stroma. In one of these patients (no. 2), there was an intracystic collection of pus. In five patients there was raised intraocular pressure; two of them showed signs of glaucoma. In three patients 'endothelial touch' was noted. The clinical course varied. In some patients there had been a stable, small cyst for years, followed by rapid growth in several weeks, sometimes leading to such complications as impairment of visual acuity or corneal touch and oedema. In the majority there has been a gradually enlarging iris cyst, which had been noted at birth, while in other patients the cyst had had a rapid growth phase, immediately after birth.

In nine patients the initial treatment was excision of the cyst. In one patient an inflamed cyst was excised after intensive topical steroid treatment had failed, and another patient required enucleation because of buphthalmos and cataract. In two patients there was a recurrence after excision, and they were subsequently treated by sector iridectomy. A 13-year-old patient (no. 10), whose stromal cyst of the right iris had been excised successfully at the age of 4 months, underwent enucleation of his right eye, which had become buphthalmic. Histopathological examination of the enucleation specimen showed evidence of severe chronic angle closure glaucoma, limbal staphylomas, iris atrophy, and buphthalmos.

The results of histopathological and immunohistochemical examination of the 11 specimens are summarised in Table 1.

Discussion

Spontaneous non-pigmented epithelial cysts arising in the stroma of the iris are uncommon

Table 1 Histopathological and immunocytochemical findings in spontaneous non-pigmented epithelial cysts of the iris stroma

Pat. no	Sex	Laterality	Age at treatment	Associated ocular findings	Treatment	Type of epithelium	Focal keratinisation	Goblet cells	W/S*	Cam 5·2	S-100	Basal melanocytes	Special features
1	M	R	53	Corneal oedema and glaucoma	Excision	Stratified squamous	+	+	++	0	0	+	
2	M	L	21	Inflammation	Steroids and excision	Stratified cuboidal	+	++	++	0	0	++	
3	M	R	4/12	Glaucoma	Excision and sector iridectomy	Stratified squamous and cuboidal	+	+++	++	0	0	+	
4	F	R	38	–	Excision	Stratified squamous and cuboidal	+	0	++	0	NA†	NA†	Hyalinised iris stroma
5	M	R	50	–	Excision	Stratified squamous	+	0	NA†	NA†	NA†	NA†	
6	F	R	19	–	Excision	Stratified squamous	0	++	++	0	0	0	
7	M	L	4/12	–	Excision	Stratified squamous	+	++	+/++	0	0	+	
8	M	R	9/12	Raised IOP, buphthalmic	Enucleation	Stratified squamous and cuboidal	0	+	NA†	NA†	NA†	NA†	Accessory lacrimal gland
9	F	L	11/12	Endothelial touch	Aspiration and excision, sector iridectomy	Stratified squamous	0	++	++	+	0	+	
10	M	R	4/12	Endothelial touch	Excision, enucleation 13 years later	Stratified squamous	0	++	+	NA†	0	0	R eye became buphthalmic
11	M	R	3/12	–	Excision	Stratified squamous	0	++	++	0	0	+	

†NA=not available.
*W/S=wide spectrum antikeratins
Immunostaining: 0=none; +=slight; ++=marked.
Cells: 0=none; +=scanty; ++=plentiful, +++=abundant.

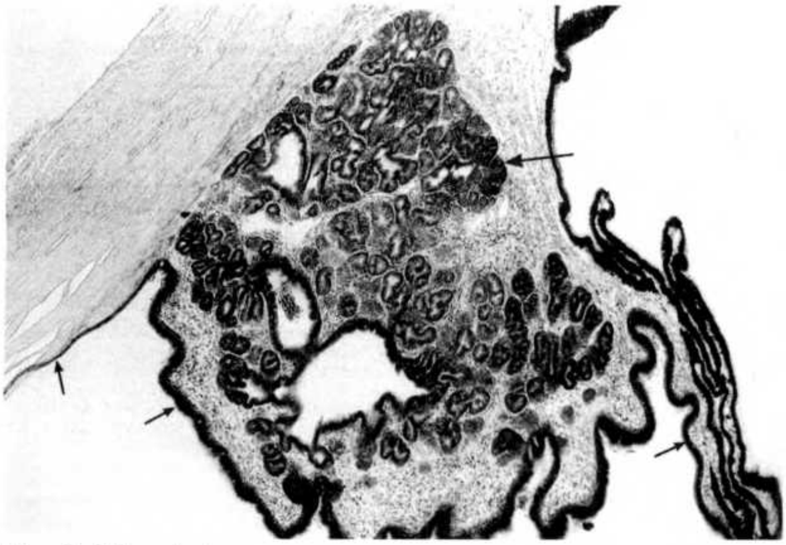
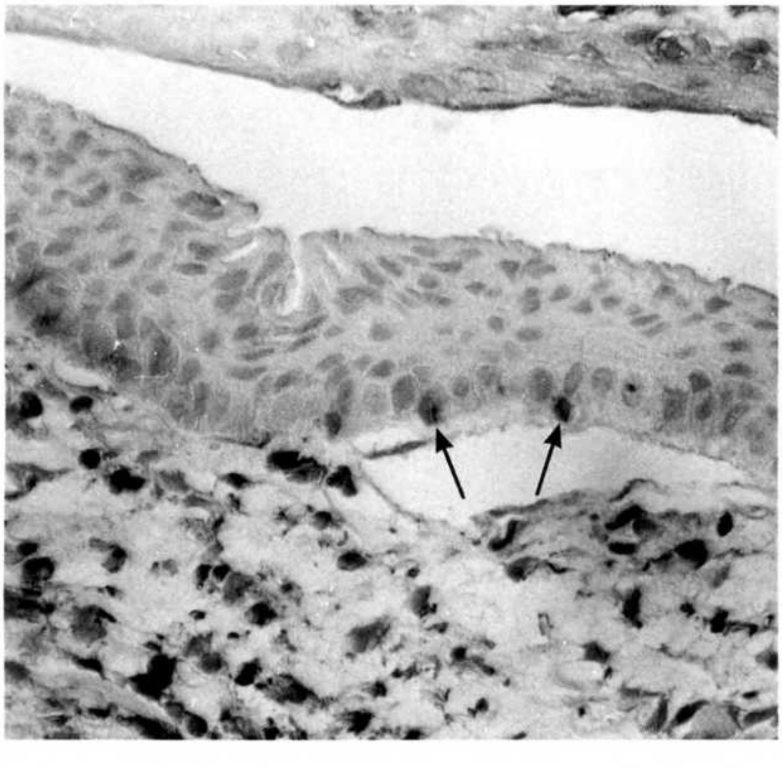


Figure 2 This enucleation specimen of a buphthalmic right eye shows ectopic lacrimal gland (large arrow) in iris stroma, adjacent to the epithelium (small arrows) of a large congenital stromal cyst, which fills the anterior chamber. (Haematoxylin and eosin, ×45.)

and little understood. Their embryogenesis has been discussed at length but remains controversial.[13-22] Although some authors[20-22] favour a mesodermal origin to account for the congenital cysts of the iris stroma, most[3-19] agree on an ectodermal origin. Ultrastructural studies,[6,12,17] demonstrating apical microvilli, desmosomes, zonula adherens and zonula occludens, and tonofilaments, show the characteristics of epithelium, but the authors could not explain the relationship between non-pigmented epithelial cells of the cysts and surrounding stromal cells.

In our series the epithelium varied from multilayered squamous to unilayered cuboidal epithelium with prominent goblet cells in the majority of cases, resembling conjunctival epithelium, which is a surface ectoderm derivative. In two cases goblet cells were not detected, which may be explained by their focal localisation in clusters.[12]

Figure 3 Antibodies to S-100 show melanocytes (arrows), neural crest derivatives, in close relation to the epithelium of the iris cyst. Dendritic melanocytes within the iris stroma are also S-100 positive. (S100, ×450.)



Most epithelial cells contain cytokeratins of varying subtypes, the expression of which depends on the type of epithelium, the degree of histological differentiation, and the state of the cell cycle. This range of expression allows limited subcategorisation of epithelia on the basis of cytokeratin profiles.[23] Higher-molecular-weight cytokeratins are typically found in complex, stratified epithelium such as that of skin, cervix, and oesophagus, while lower-molecular-weight cytokeratins tend to be present in unilayered epithelia such as renal tubular epithelium, endometrium, glandular acinar cells, and neuroendocrine cells.[23] Combinations of higher- and lower-molecular-weight cytokeratins are seen in ductal epithelia such as breast epithelium and bronchial epithelium.[23]

Staining for CAM 5·2, which detects lower-molecular-weight cytokeratin subtypes, was negative in most cases examined, except in one, which showed a mildly positive reaction. Conversely, staining with wide-spectrum screening antikeratins (Z622 and A575, DAKO), one of which (A575) demonstrates higher-molecular-weight cytokeratins, was positive in all cases. This finding is suggestive of more complex stratified epithelia, which tend to be of surface ectodermal origin.

None of the epithelial cells showed positive staining with the antibodies to S-100 antigen. However, staining with anti-S-100 was positive in the stromal dendritic melanocytes derived from neural crest. Although antibodies to S-100 are highly sensitive in detecting cells derived from neural crest such as melanocytes, their specificity is low, for they stain a variety of neural, neuroendocrine, mesenchymal, and epithelial tumours.[23] The absence of S-100 antigen in the epithelia of all cases makes an origin from the neural crest unlikely.

The histopathological and immunohistochemical findings in our study suggest that in most cases spontaneous non-pigmented epithelial cysts of the iris stroma originate from surface ectoderm. Previous immunohistochemical studies showed positive reactions to epithelial cytokeratin markers but failed to differentiate between surface ectodermal and neuroectodermal origin.[17,24] In the study by Grutzmacher *et al.*[24] two cases were examined for antigens such as muscle specific actin, smooth muscle actin, vimentin, human melanoma antigen, and S-100 protein, but no positive reaction was seen.

In one case (no. 8) an accessory lacrimal gland was seen adjacent to the cyst (Fig 2). This abnormality has been reported before,[25,26] and may in addition support the putative surface ectodermal origin of the cyst, as lacrimal gland is, like conjuctiva, a surface ectodermal derative.

Some authors who favour the theory that the cysts are derived from surface ectoderm have postulated that entrapment of ectopic tissue probably takes place at the time of formation of the lens vesicle, during the fourth week of embryogenesis.[14-16]

The S-100 antibodies showed subepithelial melanocytes, which were separated from the iris stroma by a clear basal lamina (Fig 3). Migration of neural crest cells, destined to become melanocytes, is known to occur much later in embryogenesis than lens vesiculation. The normally sited melanocytes in most cases may be evidence that ectopic conjunctival epithelium can induce normal patterns of migration of neural crest cells. In our study some iris cysts were diagnosed and treated in the second to the fifth decade of life. In the absence of a history of trauma the presence of surface ectodermal epithelium in the iris stroma in our opinion could not be explained otherwise than by developmental displacement. Spontaneous cysts which arise late in life have probably been dormant and become visible owing to a sudden engorgement, triggered by some unknown factor.

Several forms of treatment have been advocated for the management of congenital cysts of the iris stroma. Diathermy[27] and electrolysis[28] frequently cause recurrences, whereas aspiration with injection of iodine[29] or trichloroacetic acid[30] may give rise to harmful intraocular complications. In most of our patients the cysts were excised after a period of documented growth, in which the visual axis was compromised. In 20% of the patients the cyst recurred, and an additional sector iridectomy was carried out. The cyst wall should be totally removed if possible, which may require an iridocyclectomy if the ciliary body is involved.

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British Journal of Ophthalmology, 1992, **76**, 43–44

Dual appearance of fluorescein staining in vivo of diseased human corneal epithelium. A non-contact photomicrographic study

Helena M Tabery

Abstract

Adherence of fluorescein sodium dye to diseased epithelial cells, a hitherto unreported phenomenon, was captured in photomicrographs in severe herpes zoster and keratoconjunctivitis sicca keratopathies. It is notable that this phenomenon differs completely from the well known fluorescent property of the dye penetrating into defective corneal epithelium, and that the staining pattern shown by adherent fluorescein correlates well with the staining pattern shown by rose bengal dye.

Since its introduction into ophthalmology by Pflüger[1] in 1882 fluorescein has been widely used to detect corneal epithelial defects. An exhaustive review of its property of fluorescence and its use in ophthalmology has been published elsewhere.[2] The dye is believed to penetrate into damaged epithelial cells or intercellular junctions but not to stain the cells themselves.[2 3] The present study shows, however, that fluorescein also has an ability to adhere to and so to stain damaged corneal epithelial cells. This non-fluorescent phenomenon has thus far been clearly observed only in severe cases of herpes zoster and of keratoconjunctivitis sicca (KCS) keratopathy.

Materials and methods

A drop of commercially available 1% or 2% solution of fluorescein sodium (without preservative) was instilled into the temporal lower conjunctival sac in patients with various diseases of the ocular surface (herpes zoster, herpes simplex, KCS, epithelial oedema, epithelial erosions). The patients were encouraged to blink several times before and between photographs, which were taken by non-contact photomicrography, a method described elsewhere.[4] After a series of photographs a drop of 1% rose bengal (without preservative) was added, and an attempt was made to capture identical locations on the cornea. The slides, taken with Ektachrome 100 or 200 ASA film, were examined and compared under high magnification (200–400×).

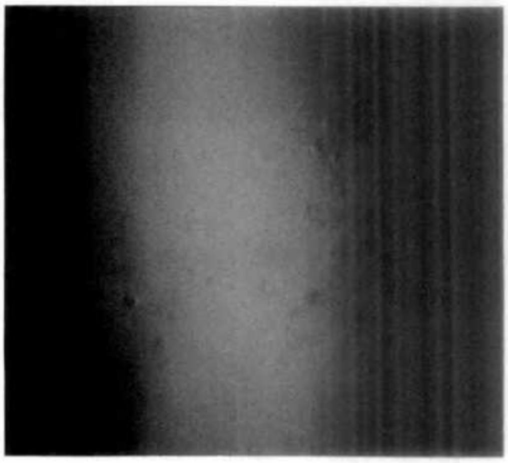

Figure 1 On retroillumination the brightly yellow hue of adherent fluorescein cannot be distinguished from dissolved fluorescein pooling in a cyst or in an epithelial defect (KCS, 1% fluorescein, retroillumination, 60×).

Results

In 12 patients with severe KCS and in four patients with severe herpes zoster keratopathy fluorescein adherence to the damaged epithelial surface was both recorded and correlated with rose bengal staining. It always appeared early after the application of the dye, and its hue varied with the mode of illumination. On retroillumination adherent fluorescein appeared brightly yellow (Fig 1) and could thus be confused with a thicker layer of dissolved fluorescein (for example when pooling in a cyst or in an epithelial defect). On focal illumination, however, the darker yellow or slightly brown hue shown by adherent fluorescein was easily distinguished from the brightly green fluorescent property of dissolved fluorescein (Figs 2a and 3a). When blue cobalt filter and focal illumination were used to enhance visualisation of fluorescence, adherent fluorescein appeared dark (Fig 2b).

The staining pattern of adherent fluorescein closely resembled that of rose bengal. That both staining patterns were basically identical became apparent by comparison of photomicrographs capturing the same area after fluorescein staining (Fig 3a) and after a subsequent rose bengal staining (Fig 3b). Indeed, rose bengal did not disclose any greater extent of damage. Some of the semi- or entirely devitalised elements indicated by adherent fluorescein were highlighted by the deep red hue of rose bengal, others stained more weakly, the resultant hue being a mixture of both. In a few the visibility of weak rose bengal staining was either precluded by the darker fluorescein background or absent. Comparison of photomicrographs also indicated that the heaviest staining by both dyes probably corresponded to the state of devitalisation: one of the stained elements disappeared between photographs, another changed position (Figs 3a and 3b).

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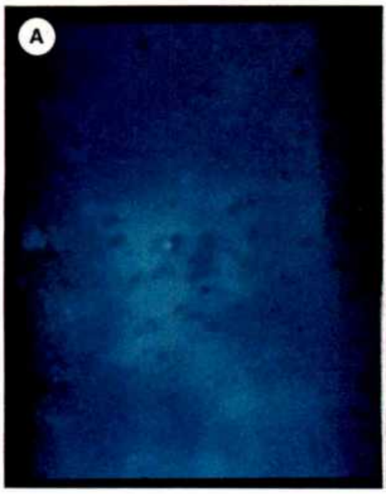


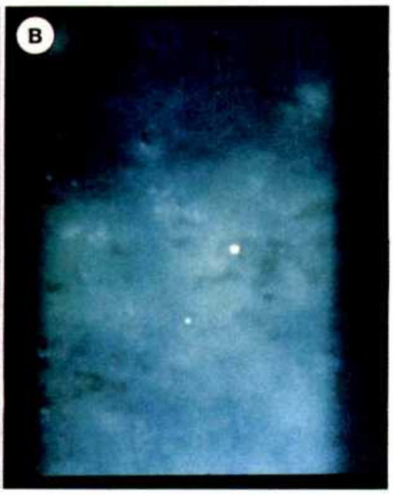
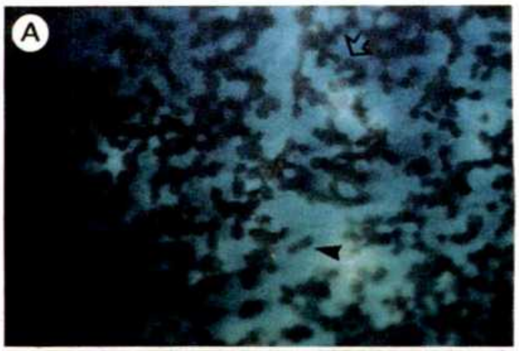


Figure 2a *On focal illumination adherent fluorescein appears darker, and the stained spots can easily be distinguished from the bright green dissolved fluorescein penetrating into the epithelium.*

Figure 2b *Compare with Figure 2a. Blue cobalt filter enhances the visibility of dissolved fluorescein; adherent fluorescein remains dark (KCS, 1% fluorescein, focal illumination, 60×).*



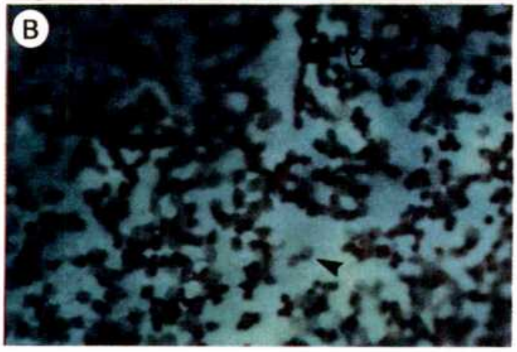


Figure 3a *Diseased elements on the corneal surface stained with adherent fluorescein show a brown-yellow hue of varying density; dissolved fluorescein appears bright green. For comparison the same spots as in Figure 3b are indicated by arrows.*

Figure 3b *Compare with Figure 3a. Subsequent staining with rose bengal shows basically the same pattern. In the original photomicrographs it is clearly visible that some of the diseased elements are highlighted by a deep red hue, others stain weakly, the hue corresponding to a mixture of both dyes; in a few no rose bengal staining is visible (arrowhead). One of the stained elements has disappeared and another one has changed position in the area indicated by open arrow (herpes zoster, 3a–2% fluorescein, 3b–1% rose bengal, focal illumination, 45×). (Original magnification in the slides 24×.)*

Discussion

The phenomenon of fluorescein sodium adherence to diseased epithelial corneal surface seems to have hitherto escaped detection in slit lamp observations. Sequential photomicrographs have shown that it is present, and that its visibility depends on the intensity of staining and on the mode of illumination, a property basically shared with other coloured objects. On focal illumination its yellow-brown hue, similar to the hue of fluorescein sodium in the dry state (for example fluorescein impregnated paper) or in a concentrated solution, can easily be distinguished from the well known brightly green fluorescent property of fluorescein dissolved in the tear fluid or penetrating into epithelial defects and cysts.

In contrast to rose bengal, which is believed to stain dead or damaged cells,[3 5] fluorescein is not believed to stain structures, even though both dyes are chemically similar, rose bengal being a derivative of fluorescein. The present study shows, however, that fixation of fluorescein occurs in a manner similar to that of rose bengal. As with rose bengal the exact nature of fluorescein bonds to the damaged cells remains unknown; in the cases presented here, both dyes seem to share a property of adherence to some devitalised, possibly keratinised elements. In other diseased states of the corneal epithelium which show rose bengal staining the absence of visible fluorescein adherence might either be real, showing differences in the chemical properties of the two dyes, or apparent, due to limitations of the observation method.

The detection of fluorescein adherence in KCS and herpes zoster keratopathies suggests that in these cases, when compared with rose bengal, fluorescein sodium is not only as good as but perhaps a more sensitive indicator of the extent of corneal surface damage. While rose bengal highlights only devitalised elements on the surface, fluorescein shows two phenomena simultaneously: fluid penetration into defective epithelium is highlighted by its fluorescence, and devitalised surface elements by its adherence.

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The optical spacer – a simple device which extends the scope of indirect ophthalmoscopy

Donald M I Montgomery

Abstract

A simple device is described which both facilitates and significantly extends the scope of indirect ophthalmoscopy.

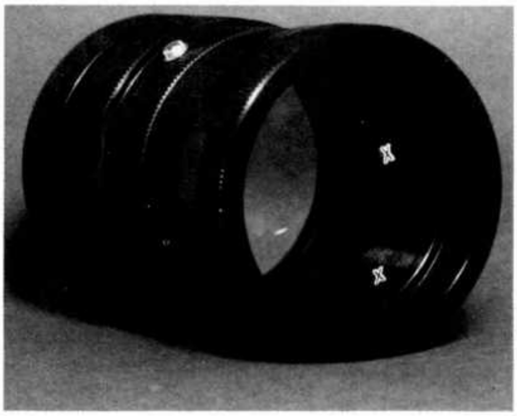

Figure 1 A prototype device showing fixation targets.

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The optical spacer is a hollow cylinder which, when coupled to an indirect ophthalmoscopy condensing lens, enables a transparent screen to be positioned at the second principal focus of the lens (Fig 1). When the fundus is observed, the retinal image is formed in the plane of the screen and can thereby be accurately localised in three-dimensional space (Fig 2). Each point on the retina in view forms an image on a corresponding point on the screen, while each point on the screen is in turn imaged upon, and therefore stimulates, its corresponding retinal point which it is seen to overlie. The ease with which stimuli may be introduced into the image plane is the key to several useful applications.

Assessment of fixation

If a patient is asked to look at a cross marked on the centre of the screen (Fig 3a) his fovea will be aligned with the cross unless his fixation is abnormal. The point and steadiness of fixation may therefore be rapidly assessed, for example, in a child with amblyopia or indeed in any condition where foveal function may be considered to be compromised.

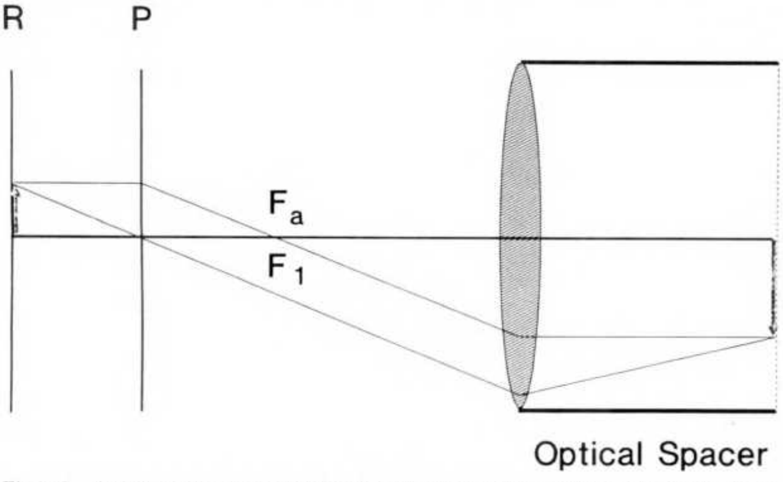

Figure 2 A transparent screen is positioned in the principal plane of the condensing lens by an optical spacer. The retina is imaged in this plane while targets introduced on to the screen are imaged on the retina. P=principal plane. F_1=first principal focus of lens. F_a=anterior focus of eye.

Fixation targets to facilitate indirect ophthalmoscopy

A fixation target in the centre of the screen allows the patient's eye to be held steady while the posterior pole is examined. If the screen and lens are now rotated about their axis while the eye fixes on a target at the margin of the screen (Fig 3a), the smooth pursuit system is exploited to enable the fundus to be scanned in one continuous movement rather than as a series of disjointed, unpredictable saccades.

Convenient recording of fundus lesions

A lesion in the fundus may be accurately recorded simply by tracing the outline of its image directly on to an acetate sheet placed upon the screen. This record may then be detached and stored in the patient's case notes. At the next attendance the previously traced outline may be again superimposed upon the lesion. Any change in size will therefore become immediately apparent (Fig 3b).

Assessment of distance visual acuity

If standard Snellen test types are photographed at 6 m with a 35 mm lens and the developed film is then centred on the optical spacer screen located in the focal plane of a +28 dioptre condensing lens, the test types, when viewed through the lens, will subtend the same visual angle as their 6 m equivalents. A convenient, portable visual acuity test is thereby produced (Fig 3c).

Visual field assessment with simultaneous funduscopy

Since each point on the optical spacer screen corresponds to the retinal point imaged at that location, it is possible to map the central visual field under direct vision by 'pointing' at the retinal image with a target pin during ophthalmoscopy while the image is stabilised by a foveal fixation target. By this means functional defects may be readily correlated with the morphological appearance of the retina. The screen may have visual angle and meridional markings to facilitate comparisons with conventional visual field charts (Fig 3d).

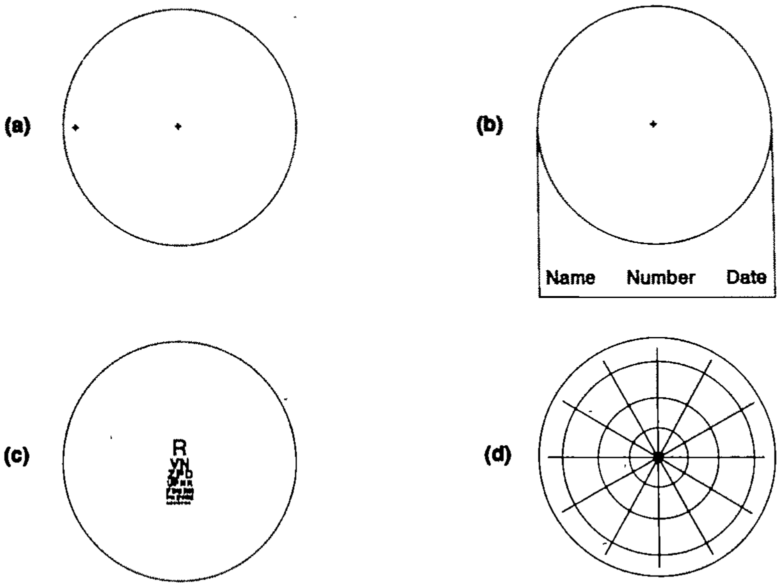

Figure 3 Selection of screens for use with the optical spacer. (a) Central target allows stabilisation of fundus image and assessment of fixation. Eccentric target enables fundus to be scanned in one continuous movement. (b) The outline of fundus lesions may be traced directly, allowing rapid recognition of change in size. (c) Portable distance Snellen acuity chart. (d) The central visual field may be explored during ophthalmoscopy, allowing functional defects to be correlated with the morphological appearance of the retina.

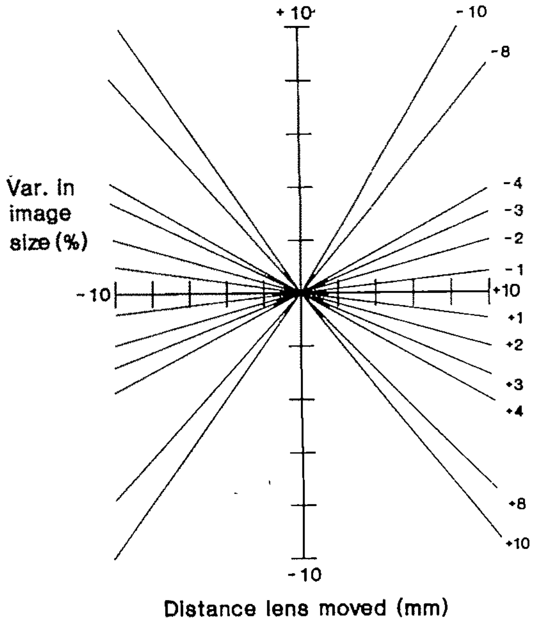

Figure 5 Variation in size of image becomes increasingly significant beyond 3 dioptres of ametropia. Distance 0 represents point at which first principal focus of lens coincides with anterior focus of eye (calculated from ray tracing based on Fig 4).

Accurate measurement of posterior segment structures and lesions

When the emmetropic eye is examined, because light rays emerging from the eye are parallel, the size of the image formed is independent of the distance of the condensing lens from the patient's eye. However, in ametropia the emergent rays are either convergent or divergent, and the position and magnification of the image will therefore be influenced by this distance (Fig 4). This effect becomes significant only at degrees of ametropia beyond about 3 dioptres (Fig 5), when it may be overcome by positioning the lens so that the first principal focus coincides with the anterior focus of the eye (as in Fig 2). With this arrangement the image, though still forming at a variable distance from the lens, always subtends the same angle at the principal focal plane. While utilising the foveal fixation target, callipers may be used to measure the stabilised image, enabling the size of the corresponding retinal object to be derived by taking into account the magnification factor of the optical system.

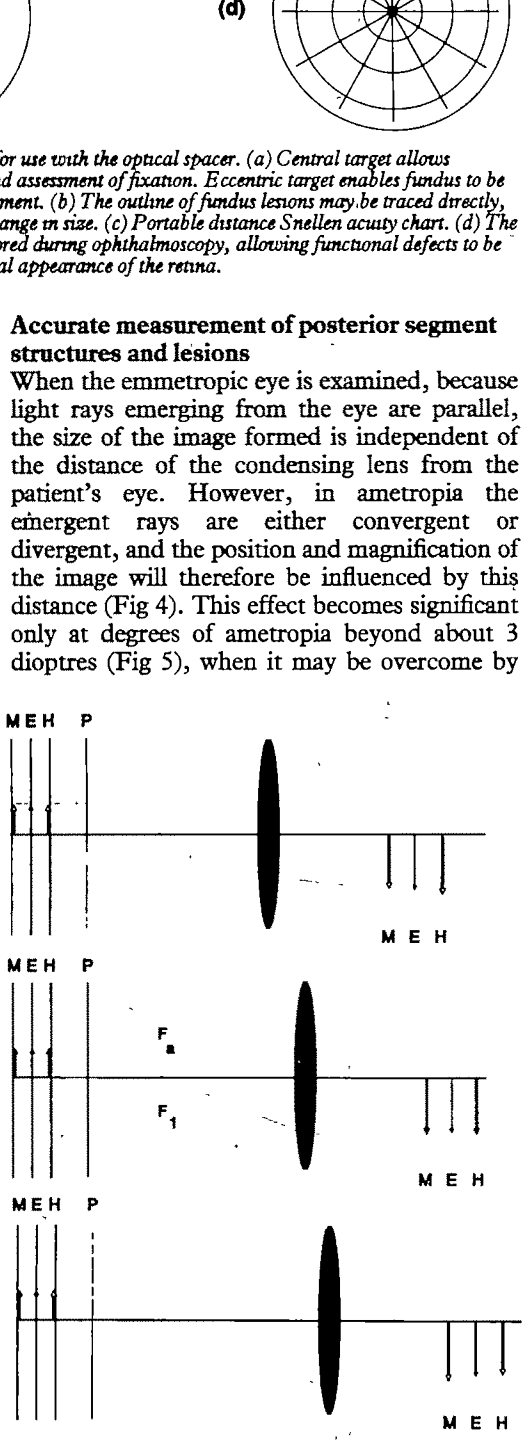

Figure 4 The effect on image size of moving the condensing lens progressively further from the eye in ametropia.
M = myopia. E = emmetropia. H = hypermetropia. P = principal plane. F_1 = first principal focus of condensing lens. F_a = anterior focus of eye.
(Adapted with permission from Elkington AR, Frank HJ: Clinical optics. Blackwell, 1984: 134.

This principle may be employed to advantage in biometry of the optic disc. The relationship between the area of the neuroretinal rim and the optic disc area has previously been shown to alter with the development of glaucoma.[1-3] Using a +15 dioptre condensing lens with the optical spacer (producing an image magnification of 4·21) and vernier callipers we can make clinical measurements of optic disc and optic cup dimensions, enabling neuroretinal rim areas to be estimated.[4] This simple technique promises to improve clinical interpretation of the optic disc in glaucoma.

Pathological lesions at the posterior pole may be measured by the same method, while measurement in the more peripheral fundus requires in addition that the wide-field retinal magnification factor be taken into account.[5]

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British Journal of Ophthalmology, 1992, 76, 47–48

MINI REVIEW

Orbital lymphoproliferative disorders

As lymphocytic tumours go, those involving the orbit are rare, accounting for just over 2% of one large series reported from a general oncology unit, and even fewer appear in the orbit as a primary event.[1] The development of lymphoid lesions in this situation is presumed to be due to either neoplasia or reactive hyperplasia. The former is amenable to low-dosage radiotherapy, whereas the latter may sometimes be combated by the administration of corticosteroids on the assumption that it is an inflammatory response, albeit to an unknown antigen. In that case it is of more than academic interest to be able to distinguish between them.

In recent years there has been an attempt, attributable in particular to Jakobiec and his coworkers, to make the distinction on immunological grounds. That the attempt has not been entirely successful has not been through any inadequacy of the methods employed but rather because of a failure, only now beginning to be rectified, to appreciate that the lymphoproliferative disorders may represent a continuous spectrum of disease that is not separable in a conceptual sense. That is to say there are grounds for regarding virtually all pure lymphocytic proliferations in the orbit as either malignant or premalignant processes.

Lymphoid lesions in this situation have something in common with extranodal lymphocytic proliferations in the gut, bronchus, and other sites, the so-called mucosa-associated lymphoid tissues (MALT).[2] A key property of this type of lymphoid tissue is that, where the lymphocytes accumulate with age, there is a predisposition for lymphomas to emerge after a long phase of localised disease.[2] The premalignant proliferation may be a polyclonal reaction to repeated antigenic challenge. The case for including orbital lymphoproliferative disease in this bracket is at present speculative, particularly as, other than the lacrimal gland, lymphoid tissue is never a 'normal' component of the orbit. It does help, nevertheless, to regard lymphocytic infiltration in this situation as a potentially progressive spectrum of disease.

LYMPHOID HYPERPLASIA

At one end of the spectrum is a benign proliferation of lymphocytes in which there is an admixture of T and B cells, the latter presenting a polyclonal immunoglobulin profile. The T cell component usually accounts for more than 60% of the lymphocyte population,[3-5] and there is reported to be a preponderance of helper as opposed to suppressor T cells in a ratio of about 5:1, which considerably exceeds the 2:1 ratio usual in normal lymph nodes and the peripheral blood.[4] Germinal centres may be seen, but, although they have usually been taken to be one of the more reliable histological indicators of a reactive lesion,[6] they are far from being an infallible guide. Prominence of the interstitial capillaries attributable to endothelial cell hypertrophy is another feature of reactive lesions, and it seems that such cells are a factor in the tendency for MALT in general to remain localised, since they are able to bind lymphocytes equipped with the appropriate surface receptors.[7]

The presence of plasma cells and histiocytes also supports the diagnosis, as does the less frequent finding of eosinophil leucocytes. If eosinophils are a significant feature, it may be that a diagnosis of Kimura's disease (angiolymphoid hyperplasia with eosinophilia) should be considered, especially if capillary endothelial hypertrophy is present.[8] Where, however, there is a conspicuously diverse leucocytic infiltrate including, possibly, polymorphonuclear neutrophils, a diagnosis of idiopathic chronic inflammation is likely to be more accurate than lymphoid hyperplasia, especially if there is an appreciable fibroblastic response. Evidence of polyclonality, as shown by immunohistochemical staining of the tissue for the presence of κ and λ light chains, is a helpful but again not infallible pointer to a reactive process.

There is no radiological distinction between reactive and neoplastic lymphoid proliferations within the orbit[9] and clinical separation is also largely impossible, though pain sometimes accompanies the inflammatory masses in contradistinction to the essentially painless lymphomas.[10]

It might be noted in passing that the term pseudotumour is a totally inadequate way of describing these lesions, especially as it can be variously taken to relate exclusively to hyperplastic lymphoid processes or to encompass the whole gamut of circumscribed orbital inflammatory disorders.[11]

LYMPHOMA

While it may be supposed that lymphomatous lesions represent the outcome of a mutation affecting a single cell, the progeny are often heterogeneous in terms of subclass expression in that they can synthesise multiple antibody heavy chains and are accompanied by a variable T cell response.[12] In the specific orbital context the T cell component is almost always less than 40%,[13] but the presence of tumour B cells with anomalous T cell markers can further confuse the picture.[14] MALT-derived lymphomas are, however, relatively homogeneous in respect of light chain expression, and evidence of oligoclonality, if not monoclonality, is a reliable index of neoplastic behaviour. Histological recognition may be possible by virtue of irregularly distributed atypical lymphocytes between the small, mature cells; commonly the former are centrocytes and centroblasts, when the prognosis following radiotherapy is fairly good. Lymphoplasmacytoid forms are also common and of similar low grade malignancy. Higher histological grades of malignancy, usually indicated by increased proportions of lymphoblasts, are less common but carry a worse prognosis.[13]

There has been some speculation on why orbital lymphomas tend to be confined to the orbit for long periods before metastasising. One possibility is that they are initially reactive lesions and only subsequently become truly neoplastic,[15] while another is that they share a feature common to several other types of extranodal lymphomas of homing back to their tissue of origin should they enter the general circulation.[2] The absence of lymphatic drainage channels might also impede dissemination.

INDETERMINATE LYMPHOID PROLIFERATIONS

There are some lymphocytic lesions within the orbit that defy ready categorisation. They may present as masses of mainly small mature lymphocytes with few, if any, of the atypical forms which would point to neoplasia. Or they may lack the mixed leucocyte composition and germinal centre formation indicative of a reactive process. In those cases where immunohistochemistry serves to demonstrate light chain restriction a diagnosis of lymphoma, usually of low grade malignancy, can be established.[10] The real difficulty arises when there is either absence of immunolabelling by light chain antibodies or, alternatively, a polyclonal pattern.

Failure to respond to immunostaining may be for technical reasons, due to a paucity of reactive groups on the lymphocytes or, conceivably, to the lesion in question being a T cell lymphoma. As yet, however, the only substantiated report of a T cell lymphoma arising within the orbit has concerned a patient in the advanced stages of an HTLV-1 related T cell leukaemia.[16] A polyclonal immunoglobulin profile taken at face value might suggest a reactive process, but clinical experience shows that many patients with this type of lesion later present evidence of dissemination and are seen to be suffering from a true lymphoma.[14,15,17] That a lymphoma should be masked in this way is understandable if it is allowed that a neoplastic proliferation may supervene in an initially reactive disorder, in which case the two processes would be operating together for a time. Examples of a sequence of this sort have been provided in respect of extranodal lymphomas in other situations, including the bronchus[18] and salivary glands,[19] and there is now good reason to believe that the same is true of the orbit. Indeed, a recent prospective analysis of some 69 patients with orbital lymphoproliferative disease casts serious doubt on the value of making a distinction between neoplastic and putative hyperplastic lesions on the basis that, while 33% of histologically diagnosed lymphomas were associated at some stage with disseminated tumour deposits, as many as 27% of hyperplastic lesions behaved in a similar fashion.[13] The validity of the histological diagnosis was inferred by an almost identical immunophenotypic analysis.

A study of five orbital lymphoid tumours that appeared to be reactive hyperplasias by light microscopy and which presented a polyclonal immunophenotypic picture showed, by means of molecular gene rearrangement analysis, that three of them were harbouring small clones of monotypic lymphocytes.[15] This is particularly interesting because it provides for an improved understanding of the lymphoproliferative disorders as they affect the orbit as a whole. Moreover, the same study revealed an overall predominance of T lymphocytes with a decided increase in the proportion of helper cells, which could mean that there is an imbalance of immunoregulatory function such that there is an ensuing undue B lymphocyte proliferation. The finding of low serum IgA levels, of slightly reduced numbers of T cells in the peripheral blood, and of circulating autoantibodies in some patients with lymphoproliferative orbital disease also suggests a disturbance of immunoregulation.[10] In these circumstances it would be conceivable that a mutation with neoplastic potential might emerge. An investigation by McCartney (personal communication, 1991) demonstrating the presence of follicle centre cells in proved lymphomas with monotypic light chain restriction adds further support to the concept of origin from a pre-existing reactive lesion.

MANAGEMENT

This is not the place for a detailed discussion of therapeutic strategy, but the information which is now available does call for some comment. Since there would seem to be cause to regard all lymphoid proliferations as potential, if not always actual, neoplastic conditions, it is probably sensible to treat all but the most obviously inflammatory lesions accordingly. The response to low doses of radiotherapy, of the order of 30 gray, has been shown to be an effective way of dissipating the apparently indeterminate lymphoid lesions as well as the undoubted lymphomas[20] and is much to be preferred to a trial course of corticosteroids given in the hope that the proliferation will prove to be inflammatory. Even so, a note of caution is appropriate, given that a minority of patients can be expected to have occult extraorbital tumour deposits which will only later become clinically manifest. Consequently, a thorough systemic investigation of every patient with an orbital lymphoproliferative mass would seem advisable.

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British Journal of Ophthalmology, 1992, 76, 49–51

CASE REPORTS

Dedifferentiated chondrosarcoma arising in the orbit

M J Potts, G E Rose, C Milroy, J E Wright

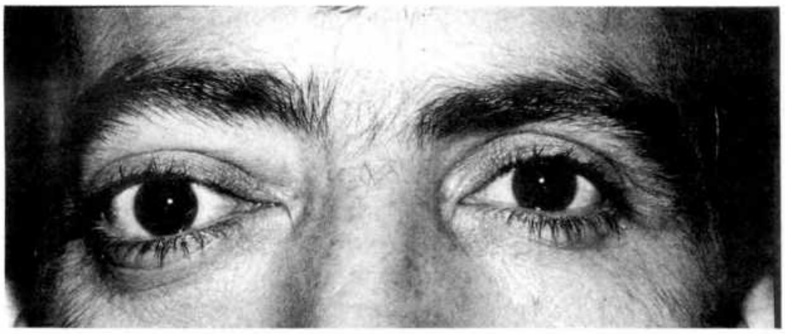

Figure 1 Chondrosarcoma limited to the right orbit, causing inferolateral ocular displacement, proptosis, and a minor degree of medial ptosis.

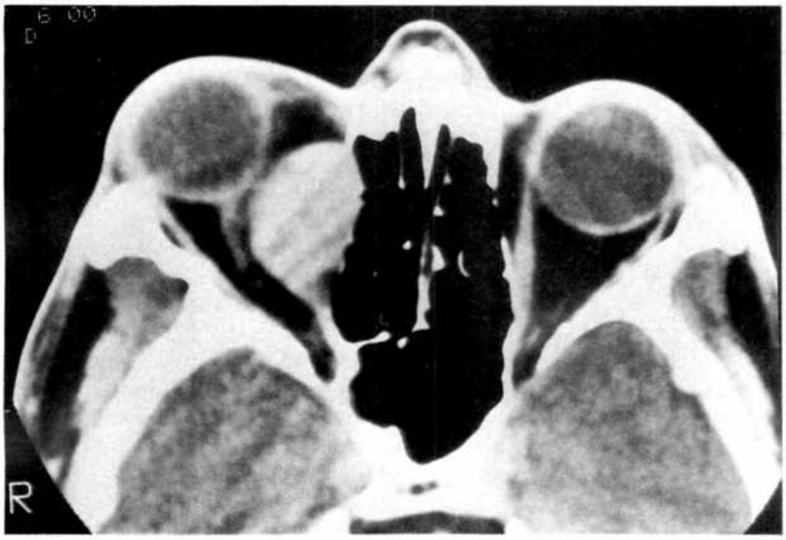

Figure 2a

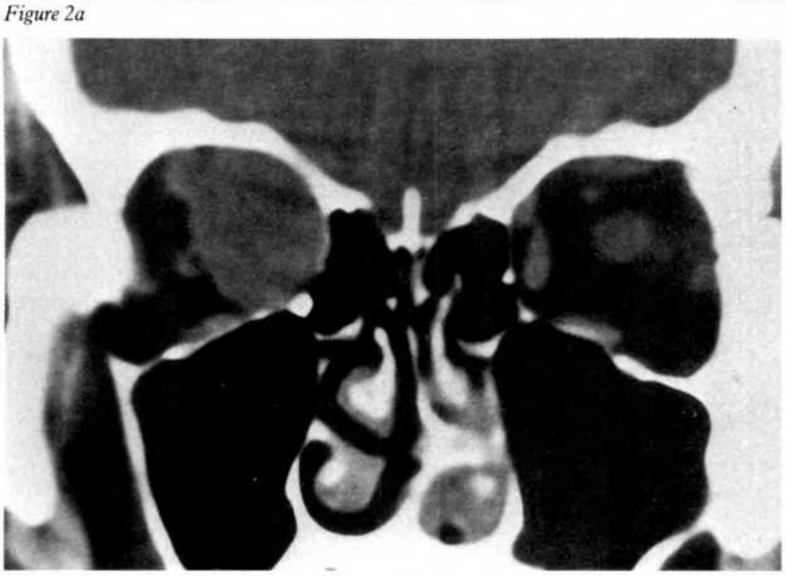

Figure 2b

Figure 2 Axial CT scan (a) shows a well-defined uniform soft tissue mass on the medial orbital wall, with no evidence of sinus involvement. Superior extension of the tumour is demonstrated on coronal scan (b).

Abstract

Orbital chondrosarcomas are extremely rare and are usually an extension of tumours involving the paranasal sinuses. A unique case of dedifferentiated chondrosarcoma arising solely within the orbit is presented.

Most chondrosarcomas arise in the axial skeleton, while extraskeletal chondrosarcomas frequently affect soft tissues of the extremities and have histologically myxoid features.[1] Chondrosarcomas of the head and neck are uncommon and generally arise from the bones of the nose or paranasal sinuses.[1-4]

We present what we believe to be the first reported case of dedifferentiated chondrosarcoma arising solely within the orbit. Chondrosarcomas confined to the orbit are extremely rare and the previously described examples have been of mesenchymal morphology; the present tumour displayed the unusual feature of histological 'dedifferentiation'.

Case report

A 33-year-old Caucasian male presented in February 1989 with a history of intermittent binocular diplopia; the frequency and severity of diplopia, characterised by vertical and oblique separation of images (especially in supraduction), having increased over 2 years. In June 1989 a superior oblique complete tenotomy was performed to relieve an abnormal head posture associated with a right-sided Brown's syndrome. Visual function at that time was recorded as normal.

Right proptosis was evident by November 1989 and the patient was referred to the Orbital Clinic at this hospital.

At referral the patient had normal visual function in both eyes. The right globe was displaced inferiorly and laterally (by 4 mm and 7 mm, respectively) and showed 7 mm of relative proptosis. All movements of the right globe were reduced, especially that of supra-laevoduction. A mass was present superiorly and medially in the right orbit, causing a minor ptosis medially with normal levator function (Fig 1). Periorbital trigeminal nerve function, the corneal reflexes and the findings on systemic examination were normal, and there was no cervical lymphadenopathy. The patient's general health was good, and there was no clinical evidence of multiple enchondromatosis (Ollier's disease).

Orbital computed tomography (CT) scans showed a soft tissue mass of uniform radio-

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lucency, situated superomedially in the right orbit and displacing, rather than infiltrating, the normal intraorbital structures (Fig 2). The well defined mass was closely applied to (and possibly arising from) the medial orbital wall, which was bowed medially; the paranasal sinuses were otherwise normal.

Anterior (external) ethmoidectomy was performed in April 1990 to provide adequate extraperiosteal access to the medial wall of the right orbit. The periosteum of the medial orbital wall was intact, without breach by extraorbital extension of the tumour. A bilobed purple, friable tumour was resected which, although separate from orbital structures, did not have a defined capsule.

There has been no evidence of tumour recurrence by 1 year after surgery.

Pathology

The tumour comprised two distinct histological patterns. Features of a cellular cartilaginous tumour were present, with cellular pleomorphism, hyperchromasia, and binucleate cells, these being features of a low-grade chondrosarcoma (Fig 3a). A highly cellular spindle cell sarcoma was evident in other parts of the tissue, with cells arranged in bundles and whorls, and with a storiform pattern in places. Mitoses were frequent in this high grade sarcoma, the tumour resembling a malignant fibrous histiocytoma (Fig 3b).

The occurrence of a malignant fibrous histiocytoma in the presence of a low grade chondrosarcoma is the typical pattern for 'dedifferentiated' chondrosarcoma.

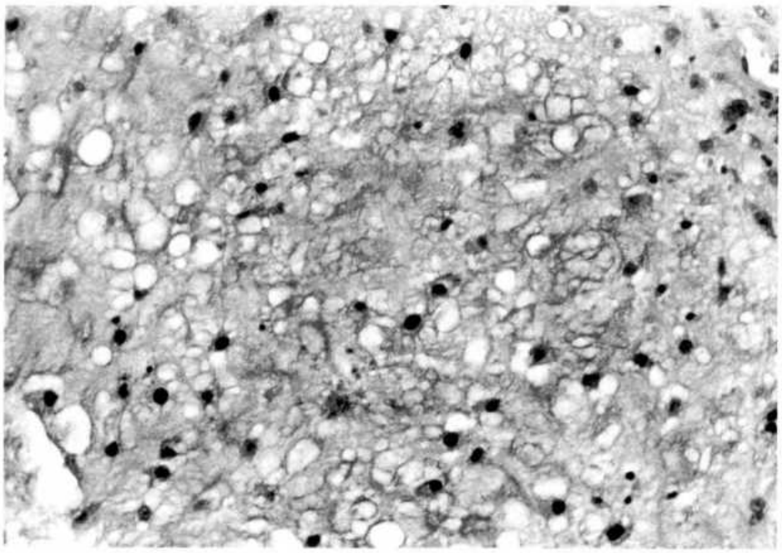

Figure 3a

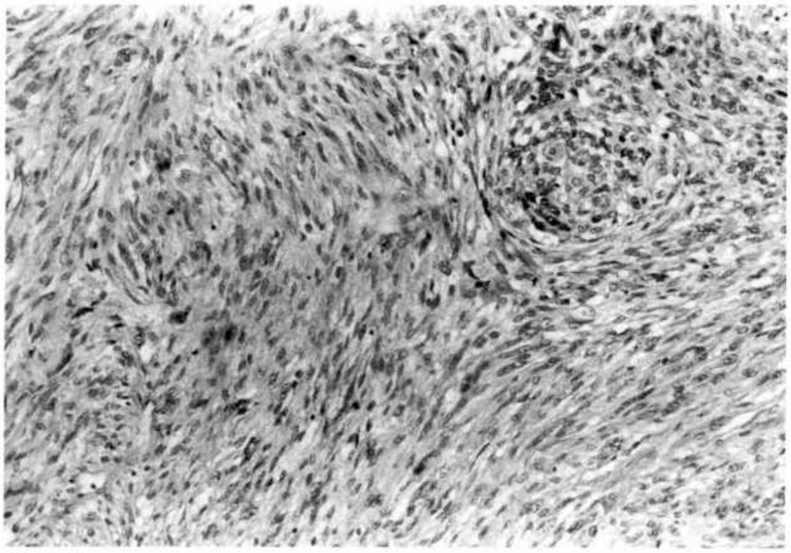

Figure 3b

Figure 3 Histopathology of dedifferentiated chondrosarcoma: sections showing features of (a) low grade chondrosarcoma and (b) high grade malignant fibrous histiocytoma. (Haematoxylin and eosin: (a) ×122, (b) ×60.)

Discussion

Chondrosarcomas outside the axial skeleton are rare and tend to occur in the head and neck. Orbital involvement is extremely rare[1-4] and is often associated with tumours affecting, or perhaps originating in, the nose or paranasal sinuses.

The tumour in the present case produced symptoms for at least 2 years before resection, although the clinical rate of tumour progression increased markedly in the 6 months before surgery. Acceleration of tumour growth, with a worsening of clinical prognosis, is commonly observed with chondrosarcomas that undergo 'dedifferentiation'.

A 'dedifferentiated' chondrosarcoma is characterised by the presence of a poorly differentiated sarcoma (Fig 3b) in an otherwise typical low grade chondrosarcoma (Fig 3a). Accelerated tumour growth is probably due to this 'dedifferentiation' of the parent tumour, with formation of a more aggressive, highly mitotic, and poorly differentiated neoplasm. The latter tumour is generally undifferentiated sarcoma, fibrosarcoma, osteosarcoma, rhabdomyosarcoma, or (as in the present case) a malignant fibrous histiocytoma.[5-7]

The prognosis for patients with chondrosarcomas is dependent on histopathological grading. Patients with low grade tumours in bone have a 78% survival at 5 years, but with tumours of moderate or higher grades the survival decreases to 53% and 22%, respectively.[8] Recurrent tumours tend to a higher, more aggressive, grade, and wide surgical excision provides the most effective primary therapy. Most chondrosarcomas respond poorly to radiotherapy or chemotherapy.

There are a number of histopathological variants of chondrosarcoma: clear cell chondrosarcomas (usually arising in bone) and myxoidchondrosarcomas (often in the extremities) both have a better prognosis that other variants. Mesenchymal and dedifferentiated chondrosarcomas have a worse prognosis, and many therapeutic combinations have been tried for these tumours.

In the head and neck the wide excision of these tumours (the treatment of choice) is often limited by vital structures; this probably contributes to a worse prognosis for tumours in these locations. Although resection in the present case appeared to be complete, treatment of tumour recurrence would be difficult. Secondary exenteration would be complicated by the previous transethmoidal resection, and the response to radiotherapy is relatively poor with high grade chondrosarcomas.

We thank the referring ophthalmic surgeons and also Professor Sir Donald Harrison for his help with the management of this patient. The illustrations were kindly provided by the Department of Medical Illustration, Moorfields Eye Hospital

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FIFTY YEARS AGO

Eye injuries among stone breakers

Among the writer's very early recollections of his childhood when he lived in the depth of the country are the village blacksmith in his smithy, the pedlar and his pack, a morose individual, the local butcher, who still wore the agriculturalists' smock frock, and the road mender breaking stones at the side of the road. The last named wore large protective goggles to avoid eye injuries. He was a formidable figure to the infant mind, and the goggles, made we believe of a fine wire mesh, added to the feeling of fear which his appearance at first sight engendered. In reality he was a most respectable member of my father's congregation and, without the goggles, very pleasant company.

We have recently been making enquiries as to the frequency of eye injuries among the flint knappers of East Anglia. This must certainly be one of the oldest occupations in the world and we are informed that injury to the eyes is exceedingly rare among them. Much of their work is done on a leather shield strapped on to the left leg above the knee, though the finer work is done on a bench. The knapper knows by long experience how to place his flint. These large flints mostly have flaws in them and the knapper percusses with his hammer with light taps until he has found the right spot and then gives a smart blow on it. Fragments appear to fly downwards and sideways and perhaps this may account for the rarity of eye injuries. This part of his work is rather different from that of the road mender whose fragment of stone lies on a bed of similar fragments, or on the ground nearby, with very little resilience beneath it. The bench work would seem more nearly to approximate that of the road mender, but so far as we could learn injury to the eye is very rare and the few knappers who still ply their trade do not wear, so far as we know, any form of eye protection.

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Periorbital necrobiosis lipoidica

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Abstract

Necrobiosis lipoidica is a granulomatous skin condition typically occurring on the legs. A patient with this condition presented with gross bilateral induration of the eyelids sufficient to close both eyes.

Necrobiosis lipoidica is a rare granulomatous dermopathy of uncertain aetiology. In about 70% of cases it is associated with diabetes.[1] Its typical presentation is of yellow, waxy, atrophic patches with purple margins on the shins. Less commonly it presents in sites away from the legs and very rarely on the face. It has been reported involving the periorbital tissues as small yellowish plaques.[2] This report is of a patient with necrobiosis lipoidica affecting all four eyelids with gross infiltration causing closure of both eyes.

Case report

The patient, a 66-year-old diabetic male, presented with both eyes closed by massive swelling and induration of the eyelids (Fig 1). Two weeks previously he had noticed small, painless, cutaneous nodules on his chin, neck, back, and shoulders. Over the next few days these lesions grew in size, and similar small nodules were noticed in the eyelids. From then on until the time of presentation all the lesions grew progressively larger and the lumps in the eyelids began to coalesce. Initially the eyelid lesions were 70–80 mm in diameter and the other lesions 30–40 mm in diameter. All the lesions (six in total) were well circumscribed, firm, non tender, prominent nodules with a typical waxy appearance and with telangiectasia round the edges. There was a slight purulent discharge from the surface of lesions round the eyes.

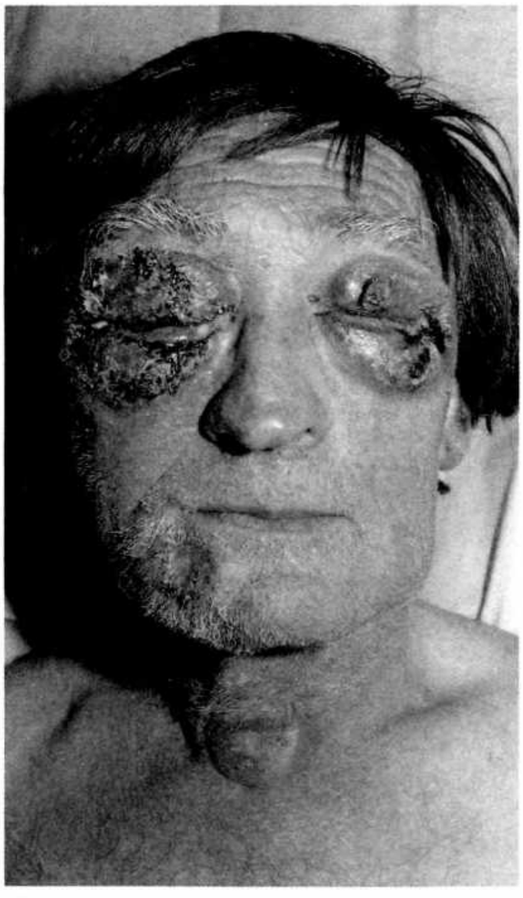

Figure 1 Appearance at presentation showing the marked lid infiltration together with other skin lesions on the chin and in the suprasternal notch.

The patient was otherwise well. He was taking chlorpropamide 300 mg once daily for his diabetes and no other medication. A general medical examination gave normal results, as did the following investigations: full blood count, erythrocyte sedimentation rate, serum urea and electrolytes, random blood glucose, chest x-ray, electrocardiogram, and liver function tests with the exception of a serum alkaline phosphatase level of 199 IU/l (normal: 35–125 IU/l). Biopsy gave the diagnosis of necrobiosis lipoidica.

The patient was admitted to a medical ward and started on intravenous flucloxacillin and fucidin and oral prednisolone 40 mg once a day. Treatment of his diabetes was changed to an insulin (Actraphane) adjustable regimen. Topical chloramphenicol was applied to the eyelids.

Intravenous antibiotics were continued for five days and the prednisolone was reduced over two weeks to 20 mg on alternate days. All the lesions began to resolve noticeably by the second day of treatment; two weeks later they were all still present but considerably better. Both eyes were now open and found to be normal.

Histopathology. The specimen revealed scattered areas of collagen necrosis. Histiocytes were diffusely intermingled throughout, and multinucleate giant cell granuloma formation was prominent. A minor degree of vascular obliteration was present (Fig 2).

Discussion

Necrobiosis lipoidica affects 0·3% of diabetics, but about 70% of cases have diabetes. It involves sites away from the legs in 15% of patients but in only 2% are the legs uninvolved. Its occurrence is unrelated to either the duration or the control of the diabetes, and women are more commonly affected than men, usually in the 35 to 45 age group.[3]

Sarcoid, foreign body reactions, and infection by Mycobacteria or fungi are other important causes of granulomatous inflammation in the

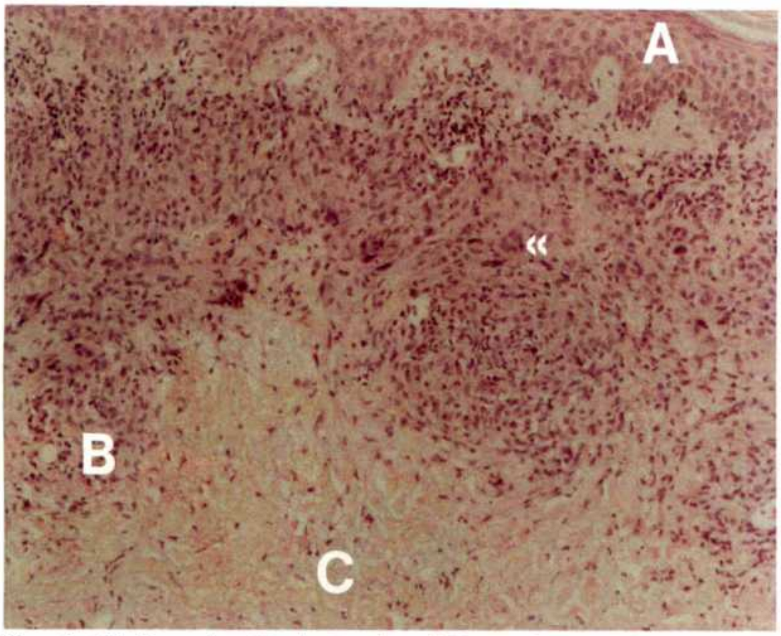

Figure 2 Skin biopsy. A=epidermis; ≪=giant cell; B=granulomatous inflammation; C=collagen necrosis (magnified ×125, H and E stain).

skin, and they may also have responded to steroid/antibiotic therapy. Histological assessment in our case, though, indicated a necrobiotic process.

Other necrobiotic skin conditions which may have a similar clinical appearance include granuloma annulare, rheumatoid and pseudorheumatoid nodules. The former is also associated with diabetes.[4]

These conditions can again be differentiated histologically, principally by the pattern of collagen necrosis, histiocyte distribution, and the extent of granuloma formation.

Usually treatment for necrobiosis lipoidica is required only for cosmetic reasons or for ulceration with secondary infection. Intralesional steroid injections and local excision have been tried with varying success.[2,5] The response to systemic steroids in our patient was dramatic, but five months after presentation the lesions are still detectable. Steroid treatment has now been stopped.

Most cases of necrobiosis lipoidica are slowly progressive and less dramatic in presentation.[6] To our knowledge such extensive involvement of the eyelids has not been reported before, and the condition should be included in the differential diagnosis of any nodular or diffuse induration of the eyelids, particularly in diabetic patients.

We thank Mr M J A Britten, consultant ophthalmic surgeon, Dr N L Reeve, consultant histopathologist, and Dr P Lewis, consultant physician, for their help in the preparation of this report.

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British Journal of Ophthalmology, 1992, 76, 54–57

A clinicopathological study of ocular involvement in primary hyperoxaluria type I*

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Abstract

We performed a clinicopathological study on the eyes of a 3-year-old girl with primary hyperoxaluria type I. An examination one year before death disclosed a slightly diminished visual acuity in both eyes with black, geographic central macular, subretinal patches. Calcium oxalate was deposited predominantly in the retinal pigment epithelium of the posterior pole, where these cells were markedly hyperplastic and hypertrophied round foci of oxalate crystals. Oxalate crystals were exceedingly sparse in other ocular structures and when present were not associated with an apparent tissue reaction in these other locations. A collagenous layer was evident between parts of the retinal pigment epithelium and the neurosensory retina, which contained occasional perivascular clumps of melanin laden cells. The predominant deposition of oxalate in the retinal pigment epithelium, with the exuberant response of these cells around the crystals, gives a clue to the pathogenic mechanisms of primary hyperoxaluria.

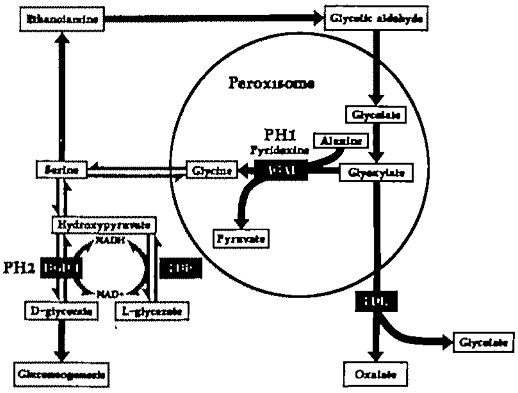

Figure 1 Metabolic pathways for primary hyperoxaluria type 1 (PH1) deficient peroxisomal alanine:glyoxylate aminotransferase and primary hyperoxaluria type 2 (PH2) deficient extraperoxisomal D-glyceric acid dehydrogenase. DGDH=D-glyceric acid dehydrogenase, LDH=lactate dehydrogenase. AGAT=alanine: glycoxylate aminotransferase. NADH=reduced nicotinamide adenine dinucleotide. NAD+=nicotinamide adenine dinucleotide.

Calcium oxalate crystals may be deposited in the kidneys, eyes, bones, joints, skin, cardiac conduction system, and other tissues as a primary or secondary phenomenon. The term primary hyperoxaluria (primary oxalosis) refers to two rare genetic inborn errors of metabolism characterised by nephrocalcinosis, recurrent calcium oxalate nephrolithiasis, and an excessive urinary excretion of oxalic acid. Early diagnosis can be suspected by the finding of increased echogenicity of the renal papillae on ultrasonography before nephrocalcinosis is detectable on routine roentgenograms of the abdomen. Primary hyperoxaluria may be particularly severe when it presents during infancy with acute renal failure.

Primary hyperoxaluria type I (McKusick 259900) (glycolic aciduria) is typified by an excessive urinary excretion of glyoxylic and glycolic acids and is due to a deficiency of alanine:glyoxylate aminotransferase (AGAT) (Fig 1). The AGAT gene has recently been sequenced[1] and the mutation predicted to cause the disease in one-third of all patients with primary hyperoxaluria type I has been identified. The manifestations of primary hyperoxaluria type I vary markedly.[2] This autosomal recessive disease usually becomes clinically evident during childhood or early adulthood with urolithiasis leading to end stage renal failure. A retinopathy characterised by tiny yellow glistening specks ('flecked' retina, crystalline retinopathy) or by large black geographic submacular lesions has been noted in one-third of patients with primary hyperoxaluria type I.[3-13] End stage renal failure has invariably preceded or occurred concurrently with this funduscopic appearance, which has usually been limited to the posterior pole.

In a clinical series of 24 patients with primary hyperoxaluria we have previously shown the extreme clinical variability in the funduscopic appearance.[13] One of the patients from our series died, and in this communication we report the histopathological findings in the two eyes that were obtained post mortem and compare them with those in previous studies.

Case report

The patient, a girl, was born weighing 3912 g, after an uncomplicated pregnancy and delivery to a healthy primigravida mother. She was healthy and developed normally until 8 months old, when she presented with weight loss, anorexia, and lethargy and was found to have primary hyperoxaluria type I with anuric renal failure. Treatment was begun with intensive haemodialysis, supplemental pyridoxine, electrolyte manipulations, and dietary restriction of oxalate and ascorbate according to our previously described protocol.[14] At 15 months of age a renal transplantation was performed with a living relative as a donor.

The patient gradually developed recurrence of calcium oxalate in her renal graft and died two years later of renal failure. At 2 years of age we performed an ophthalmic examination, which has been previously reported[13] (Fig 2). An electroretinogram was normal.

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*Presented in part at the International Society of Ophthalmic Pathologists, New Orleans, LA, USA, October 1989.

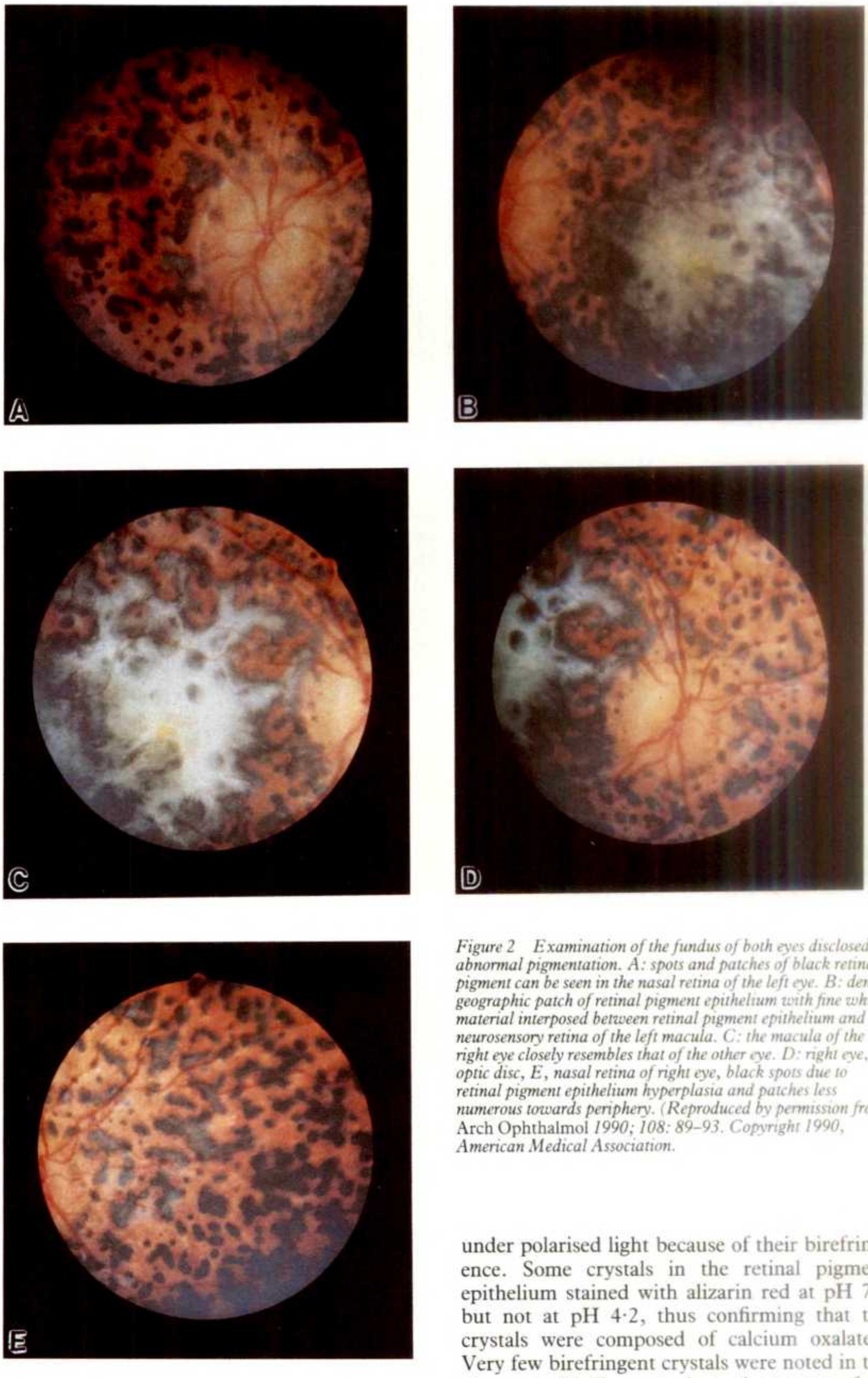

Figure 2 Examination of the fundus of both eyes disclosed abnormal pigmentation. A: spots and patches of black retinal pigment can be seen in the nasal retina of the left eye. B: dense geographic patch of retinal pigment epithelium with fine white material interposed between retinal pigment epithelium and neurosensory retina of the left macula. C: the macula of the right eye closely resembles that of the other eye. D: right eye, optic disc, E, nasal retina of right eye, black spots due to retinal pigment epithelium hyperplasia and patches less numerous towards periphery. (Reproduced by permission from Arch Ophthalmol *1990; 108: 89–93. Copyright 1990, American Medical Association.*

Results

Histopathological examination of the eyes disclosed numerous, pitch black foci in the posterior portion of the fundus (Fig 2). By light microscopy these dense black foci consisted of multiple layers of hyperplastic and hypertrophic retinal pigment epithelium (Fig 3). Numerous calcium oxalate crystals were present within the clumps of retinal pigment epithelial cells and were dramatically demonstrated when viewed under polarised light because of their birefringence. Some crystals in the retinal pigment epithelium stained with alizarin red at pH 7·0 but not at pH 4·2, thus confirming that the crystals were composed of calcium oxalate.[15] Very few birefringent crystals were noted in the pigment epithelium anterior to the equator of the eye. A collagenous layer was evident on the surface of some reactive retinal pigment epithelial cells in the macula. Choroidal neovascularisation was not present.

Most of the overlying neurosensory retinal and other ocular structures were normal except for autolytic degeneration of the photoreceptors.

Liver tissue, analysed by Professor C Danpure, showed no alanine:glyoxylate aminotransferase activity, confirming the diagnosis of primary hyperoxaluria type I.

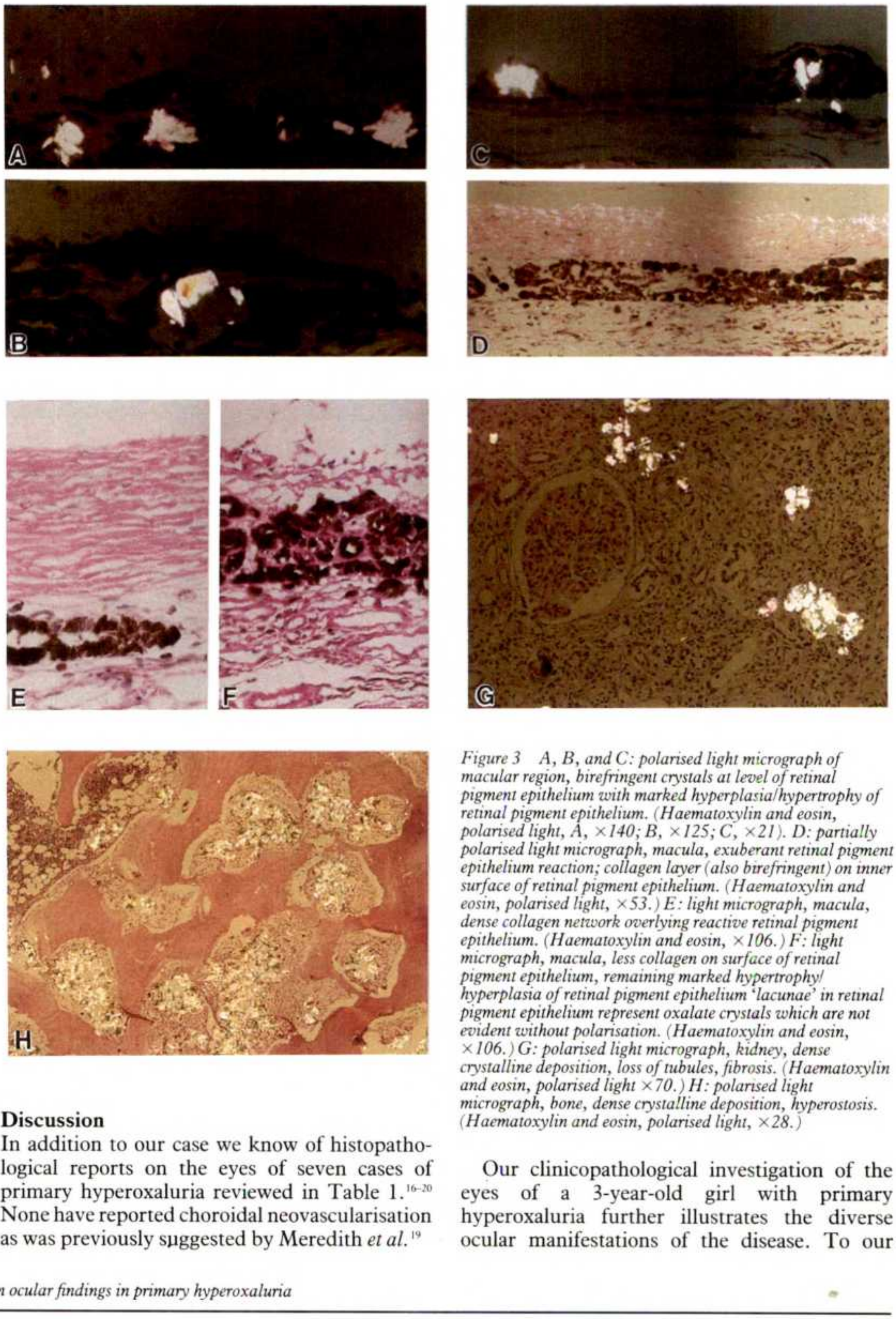

Figure 3 A, B, and C: polarised light micrograph of macular region, birefringent crystals at level of retinal pigment epithelium with marked hyperplasia/hypertrophy of retinal pigment epithelium. (Haematoxylin and eosin, polarised light, A, ×140; B, ×125; C, ×21). D: partially polarised light micrograph, macula, exuberant retinal pigment epithelium reaction; collagen layer (also birefringent) on inner surface of retinal pigment epithelium. (Haematoxylin and eosin, polarised light, ×53.) E: light micrograph, macula, dense collagen network overlying reactive retinal pigment epithelium. (Haematoxylin and eosin, ×106.) F: light micrograph, macula, less collagen on surface of retinal pigment epithelium, remaining marked hypertrophy/hyperplasia of retinal pigment epithelium 'lacunae' in retinal pigment epithelium represent oxalate crystals which are not evident without polarisation. (Haematoxylin and eosin, ×106.) G: polarised light micrograph, kidney, dense crystalline deposition, loss of tubules, fibrosis. (Haematoxylin and eosin, polarised light ×70.) H: polarised light micrograph, bone, dense crystalline deposition, hyperostosis. (Haematoxylin and eosin, polarised light, ×28.)

Discussion

In addition to our case we know of histopathological reports on the eyes of seven cases of primary hyperoxaluria reviewed in Table 1.[16-20] None have reported choroidal neovascularisation as was previously suggested by Meredith *et al.*[19]

Our clinicopathological investigation of the eyes of a 3-year-old girl with primary hyperoxaluria further illustrates the diverse ocular manifestations of the disease. To our

Table 1 Pathological reports on ocular findings in primary hyperoxaluria

								Pathological findings	
Case	*Reference*	*Years*	*Age at onset of symptoms*	*Renal failure*	*Renal transplant*	*Age at death*	*Funduscopic findings in posterior pole*	*Crystal locations*	*RPE hyperplasia*
1	Scowen *et al*[16]	1959	1 year	Yes	No	23 years	Not described	Ciliary body (scanty)	No
2	Timm[12]	1963	Childhood	Yes	No	23 years	Not described	Extraocular muscles, lacrimal glands, ciliary body, choroid, retina, optic nerve (especially vessels)	No
3	Timm[11]	1976	Not stated	Yes	Yes	26 years	Flecked retina	RPE, sensory retina, ciliary body	No
4	Toussaint *et al*[17]	1976	10 years	Yes	Yes	33 years	Flecked retina	RPE ciliary body	No
5	Fielder *et al*[18]	1980	5 months	Yes	No	6 months	Fleck retina	RPE	No
6	Meredith *et al*[19]	1984	6 months	Yes	No	7 months	'Ring of yellowish lesions'	RPE, iris sensory retina, ciliary body, conjunctiva	No
7	Speiser *et al*[20]	1988	4 months	Yes	No	3 years	Black ringlets	RPE sensory retina	Mild
8	Small, Scheiman, Klintworth	1991	9 months	Yes	Yes	3 years	Black geographic lesions	RPE	Marked

RPE=retinal pigment epithelium.

knowledge this is the first histopathological report of a patient with enzymatically confirmed primary hyperoxaluria type I. In contrast to previously reported cases, the eyes of our patient were characterised by: (1) an exuberant retinal pigment epithelial reaction round the crystals which was seen funduscopically as geographic black lesions; (2) the collagenous layer between the retinal pigment epithelial cells and the neurosensory retina which correlated with the clinically apparent thin white layer located between the neurosensory retina and the retinal pigment epithelium; and (3) the paucity of oxalate crystals in the remaining ocular structures.

We acknowledge the pioneering biochemical and molecular genetic work of Christopher Danpure on this disease and thank him for performing the enzyme assays on our patient

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British Journal of Ophthalmology, 1992, **76**, 58–60

Vitelliform macular degeneration associated with mitochondrial myopathy

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Abstract

A patient with mitochondrial myopathy is described. Examination of his fundus revealed bilateral vitelliform degeneration of the maculae. This lesion is a focal abnormality of the retinal pigment epithelium and may be a manifestation of the underlying mitochondrial disease.

The mitochondrial myopathies (MM) or cytopathies or encephalomyopathies, as they are variably described, are a group of disorders with marked clinical and biochemical heterogeneity. The brain and muscle are the principal tissues that are affected, but involvement of haemopoietic, endocrine, cardiac, liver, and ocular tissues is well recognised.[1] Diagnosis of these conditions is based on the demonstration of morphological abnormalities of mitochondria on skeletal muscle biopsies; identification of biochemical defects, mainly along the respiratory chain; or as has been described recently by identification of abnormal or mutant mitochondrial (mt) DNA by means of restriction fragment length polymorphisms and DNA sequencing.[1-3]

The basis of the heterogeneity is explained in terms of the mitotic segregation hypothesis, whereby it is proposed that each cell contains a proportion of wild type and mutant mt DNA.[4-6] When the relative proportion of mutant mt DNA is present at a critical threshold in a selected tissue, clinical disturbance of that tissue will result.[3-6] This proportion of mutant mt DNA is transmitted maternally and is distributed by mitotic segregation at the time of zygote formation.[3-6]

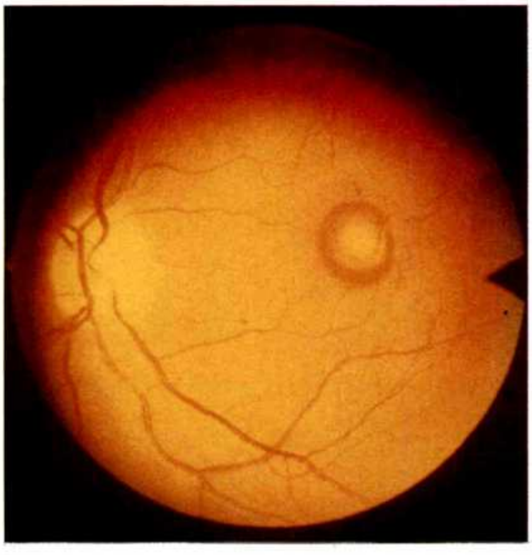

Figure 1 Photograph of the patient's right fundus showing the typical 'egg yolk' appearance diagnostic of vitelliform degeneration of the macula. The optic disc and vasculature are normal. No pigmentary retinopathy is present.

In this paper we describe the occurrence of vitelliform macular degeneration in a patient with infantile mitochondrial myopathy. The possible significance of this association is discussed.

Case report

A 20-year-old black male patient presented with symptoms of a multisystem disorder. He was of short stature (height 145 cm) and had marked mental impairment. The essential findings were those of a proximal myopathy with a cardiopathy; ptosis without ophthalmoplegia; bilateral sensorineural deafness; distal symmetrical sensory neuropathy; and raised concentration of cerebrospinal fluid protein (0·5 g/l). He had no dysmorphic features but showed evidence of delayed sexual maturation. Funduscopy revealed normal optic discs but striking vitelliform changes of the maculae (Fig 1). Biochemically the main abnormalities were those of a raised resting serum lactate (2·8 mmol/l; normal=0·16–1·8 mmol/l) and a raised serum pyruvate (83 mmol/l, normal=41–67 mmol/l). A biopsy of the left biceps brachii showed that an estimated 10% of the fibres were 'ragged red' on the modified Gomori-trichrome stain (Fig 2a). Subsarcolemmal accumulations of mitochondria were noted on NADH-reductase stain. Cytochrome oxidase and phosphorylase activity was found to be normal with the appropriate stains for these enzymes. Electron microscopy revealed elongated and oval shaped mitochondria containing laminated paracrystalline inclusions (Fig 2b).

Discussion

Pigmentary retinopathy in association with mitochondrial myopathies (MM) is well described.[1 7] Three patterns of retinopathy, namely, a 'salt and pepper' type, a retinitis pigmentosa type, and atrophy of the retinal pigment epithelium (RPE) have been described.[7] Approximately 36% of patients with mitochondrial myopathies have involvement of the RPE, with the salt and pepper type being the commonest.[7] The reasons for involvement of the RPE are not clear. The RPE contains large numbers of mitochondria, in keeping with its high energy state.[7] Enlarged mitochondria and widespread loss or atrophy of the RPE in patients with MM have been described.[7] However, the RPE mitochondria have not been studied in a functional manner in patients with MM, and biochemical abnormalities of muscle mitochondria described in patients with MM have not been reported in the RPE mitochondria.[7]

Vitelliform macular degeneration is recog-

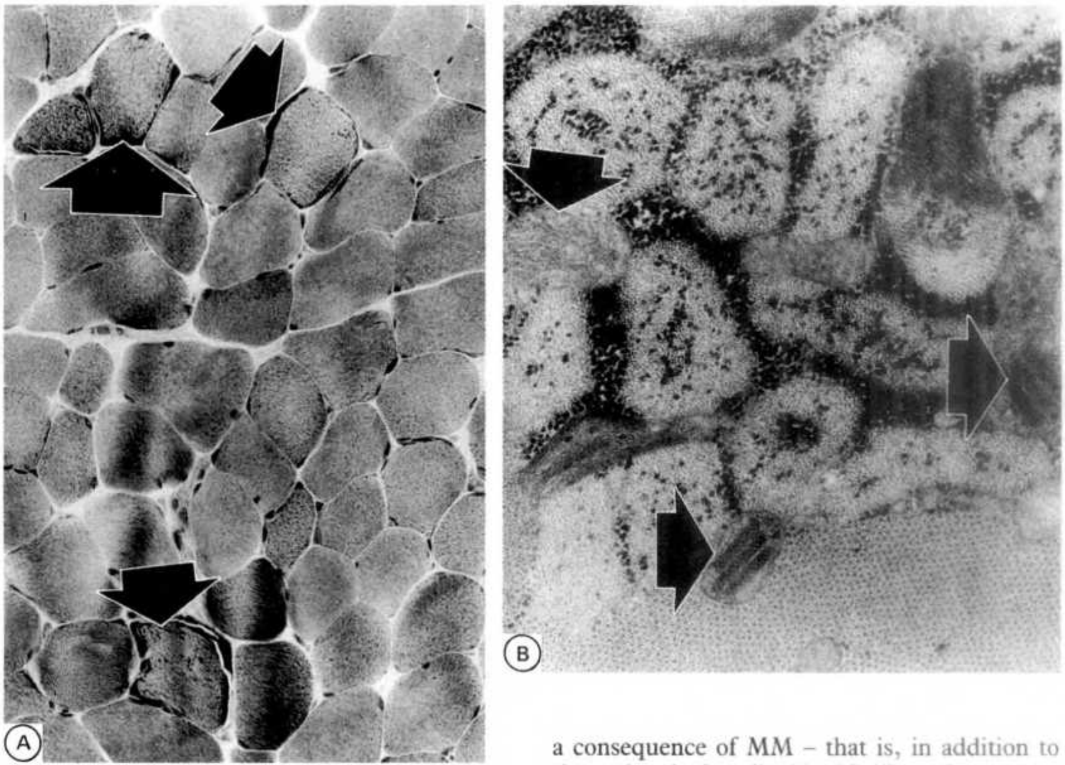

Figure 2 A: Gomori-trichrome stain of a section of the patient's muscle biopsy (biceps brachii) showing ragged red fibres with subsarcolemmal accumulation of mitochondria (arrows). B: Electron micrograph showing oval shaped mitochondria, with laminated paracrystalline inclusions (arrows). (×42 000.)

nised by its characteristic 'egg yolk' appearance.[8] It is typically present in Best's disease, an autosomal dominant hereditary macular disease.[8,9] In this disease the classical vitelline lesion, which is encountered infrequently, occurs focally in the region of the macula, but may occur multifocally and in extramacular sites.[10] The lesions may be present uniocularly and occur asymmetrically.[10] Diagnosis often requires the establishment of an autosomal dominant mode of inheritance as well as the demonstration of an abnormal electro-oculogram (EOG).[8-10] The EOG is invariably abnormal in all affected members and carriers, and is abnormal in both eyes in cases where the lesion is uniocular. The abnormality in the EOG indicates that the disorder affects the RPE in a widespread manner and is not specifically a macular response.

Vitelline lesions may also occur in patients with a normal EOG and no evidence of a dominantly inherited maculopathy. These pseudovitelliform lesions occur in adults and have been associated with perifocal retinal capillary leakage, RPE and neurosensory detachments, or non-specific pigmentary changes. In these instances the vitelliform lesion is postulated to occur as a result of an acquired macular degeneration.[10]

The finding of vitelliform macular degeneration in a patient with MM is therefore remarkable, and raises several possibilities regarding the reasons for the coexistence of these two uncommon diseases. The first is that this is a chance association of two rare disorders. The inheritance pattern of the MM is maternal,[3-5] whereas vitelliform macular degeneration, as it occurs in Best's disease, obeys nuclear Mendelian genetics.[8,9] It is our contention, however, that vitelliform macular degeneration is a further atypical form of RPE abnormalities that occur as a consequence of MM – that is, in addition to those already described by Mullie *et al.*[7]

In support of this contention is the observation of macular degeneration in a patient with mitochondrial encephalomyopathy and brain infarctions described by Kuriyama *et al.*[11] These authors described their patient as having a 'well demarcated white-yellow circular spot that resembled an egg-yolk'. While no photograph of the lesion is shown, this description is typical of vitelliform macular degeneration. We therefore consider that the association with MM is unlikely to be a chance finding. The degeneration would thus be due to widespread mitochondrial dysfunction in the RPE. This would be in keeping with the abnormal EOG found in this disorder, which reflects the widespread involvement of the RPE. The reasons for the focal macular presentation are unclear but, in terms of the MM, one may speculate that differential distribution of mitochondria containing mutant mitochondrial DNA in the RPE would account for both focal macular and extramacular lesions. Further clinical and pathological analyses are important to determine the nature of this association.

With respect to Best's disease, the question that arises from the discussion above is whether or not it is a disorder of mitochondrial dysfunction. The autosomal dominant nature of the condition does not preclude it from being caused by mitochondrial disease. The concept of nuclear factors or genes influencing mitochondrial functions, with the resultant disease appearing to follow Mendelian genetics, has been proposed by several authors.[1-5] Family pedigrees of patients with MM have been shown to follow dominant or recessive modes of inheritance.[1-5] In the case described here there was no clinical vitelliform macular degeneration in the patient's mother or step-sister. The grandmother has senile maculopathy, which can be difficult to distinguish from long standing vitelliform degeneration.[9] We were unable to examine other family members or carry out EOG examinations. Kuriyama *et al*[11] also do not give details of family members in their case. Further investigations of established pedigrees of Best's macular dystrophy are therefore needed.

The authors thank Dr V Fabian, Department of Pathology, University of the Witwatersrand, Johannesburg, for her assistance with the histology and electron microscopic findings. Our thanks also to Mrs B Pelser and Mrs J Gagu for typing the manuscript.

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LETTERS TO THE EDITOR

Trachoma still undefeated

Sir,—Your interesting editorial[1] about problems still outstanding in the study of trachoma was drawn to my attention recently and revived personal memories of this disease. Having spent a substantial part of my working life in various tropical countries I have seen and treated a large number of cases in various stages of the disease.

In August 1939 as the very junior regimental medical officer of an Indian battalion under embarkation orders for the Middle East, in the course of a pre-embarkation medical inspection, I found that some 80% of the Sikh company had trachoma, these men were all from the Punjab in north west India. The disease was relatively inactive but the question of fitness for active service arose. On the eve of war, the whole battalion's move might have been delayed due to the unfitness of virtually one whole company. This was a matter for a more senior opinion than mine and the station ophthalmic specialist was sent to cover me. He confirmed the diagnosis and passed them all 'fit.' The battalion went to North Africa but I was diverted to Burma so I was unable to follow their fortunes. Subsequent experience of trachoma among Indian troops convinced me that the hygienist had been right to pass them fit. Trachoma was fairly common in the Indian Army especially among soldiers recruited from the dry, dusty, northern parts of the country. In the high state of hygiene in which they lived, even on active service, few developed serious complications. It seemed therefore that there must be other factors causing the development of those complications which often cause blindness, notably entropion and gross corneal pathology.

I next met the disease in its endemic form as ophthalmic specialist in the Gold Coast, as it was then called, from 1948–52. From a combined analysis of cases seen personally, in the eye clinic of the Gold Coast Hospital in Accra and on tour in the Northern Territories, I was able to show that the incidence and severity of the complications of trachoma were far greater amongst the inhabitants of the dry dusty Northern Territories than those in the coastal area.[2] At that time facilities for pathological and bacteriological investigation were limited so findings were based on clinical observation.

From 1961 to 1966 I was working in the Jane Furse Anglican Mission Hospital, a large hospital in Sekukhuniland, a very dry dusty area of the Northern Transvaal. Once again I was struck by the high incidence of trachoma, commonly complicated by entropion and ultimate blindness. Thanks to the interest and help of Dr A Davies, the Medical Superintendent and Pathologist at the hospital, it was possible to demonstrate in some of the more severe cases, an accumulation of silica in the scarred conjunctiva and superior tarsi removed at operation.[3] Those Africans who had spent long periods working in the gold mines away from Sekukhuniland rarely went blind from the later complications of trachoma. These men had lived in barracks where hygiene standards were high and water plentiful.

During my last overseas appointment I spent two years as a government ophthalmic specialist in the two main government hospitals in the coral island of Mauritius in the Indian Ocean. The population, then about 860 000, consisted of several settled communities, in descent mainly Indian, European, African, Chinese or a mixture of these. I have no figures for the total number of ophthalmic cases seen but some idea may be deduced from the fact that I performed just under 1600 cataract extractions during the two years in the island. Mauritius is based on coral and remarkably free from dust. I did not see a single case of trachoma.

Most of the sociodemographic risk factors in all the rural areas in which I worked were in my opinion similar to those described in a rural Egyptian village.[4] Proper latrine facilities should reduce the fly density and one mode of transmission during the infective stage of the disease. However, if our findings in the Transvaal, of silica deposits in the tarsal conjunctiva in more advanced cases can be repeated in other areas, then there would be evidence that provision of adequate washing facilities as well as latrines may be equally important.

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1 Trachoma still undefeated [Editorial] *Br J Ophthalmol* 1991; 75: 321
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Penetrating keratoplasty for keratoconus

Sir,—I would like to congratulate Sharif and Casey on an excellent description of the long-term success of penetrating keratoplasties for keratoconus.[1] However, their study design may have underestimated the probability of graft failure. Figure 4 shows the Kaplan-Meier survival curve of their 100 grafts during the course of the study. They found most failures occurred in the first 500 days (1·37 years). In their materials and methods section, they state only keratoconus patients with a minimum of 4 years' follow up were included in the study. It would therefore appear that the only failures included were those that kept coming back with a failed cornea for some reason, or those that had been regrafted and followed for the minimum of 4 years. Patients having failed corneas without retreatment and being lost to follow up before 4 years would have been excluded in their study design. It has been my experience that some patients with failed corneal grafts do not have a regraft and are not interested in follow up. Though I suspect their success rate will still be quite high, it would be interesting to know how many total keratoplasties for keratoconus were performed during the study period, and how many of those that did not reach 4 years of follow up had failed corneal grafts or episodes of rejection.

As their data pointed out, a large portion of individuals undergoing corneal transplant surgery for keratoconus are young males. As a group, young males are more prone to be involved in activities that could lead to traumatic rupture of the graft wound with loss of the graft or even the eye. They are also more prone to be lost to follow up, either because of relocating or by being inattentive to the care of their eye. The overall number of these individuals having adverse events may be small but could still significantly change the survival data.

Their study appears to be an important one which provides excellent information on many of the long-term complications and outcomes of eyes having penetrating keratoplasty for keratoconus. However, in order to have an accurate survival analysis all consecutive cases performed during their study period would need to be included.

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1 Sharif KW, Casey TA Penetrating keratoplasty for keratoconus: complications and long-term success *Br J Ophthalmol* 1991; 75: 142–6

Sir,—We would like to thank Dr Price for his compliments and thoughtful remarks on our paper.[1]

The total number of penetrating keratoplasties for keratoconus performed in our unit during the study period was 148; 100 of these cases were included in the study as they fulfilled our criteria of a minimum follow-up period of 4 years.

The aim of the study was to determine the long-term survival of the grafts, so the remaining 48 cases (with shorter follow-up periods) were excluded from the study. Analysis of this subgroup was carried out and it showed that the average follow-up period was 2 years. Forty five grafts (out of 48) were still clear at the end of the follow-up period (93·7%). Two of the three graft failures occurred secondary to irreversible rejection episodes and the third graft suffered a primary graft failure Thus, this survival analysis of the unpublished subgroup shows similar findings to those detected in our study with long-term follow-up.

The other point raised by Dr Price was in relation to the male predominance in our study (68%), and the possibility that this could change the survival data.

Further analysis of all the 148 keratoplasties revealed that traumatic wound dehiscence occurred in four cases only; two of which were females (ie male to female ratio was 1:1). Out of the 48 cases, who were lost to follow-up within the first 4 years postoperatively, 25 were females (52%). Contrary to Dr Price's suggestion, all these findings support our initial observations that male to female ratio in our study did not significantly influence the survival data.

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1 Sharif KW, Casey TA Penetrating keratoplasty for keratoconus: complications and long-term success *Br J Ophthalmol* 1991, 75· 142–6.

Diabetic radiation morbidity

Sir,—Features of ocular radiation vasculopathy were first described in 1933 and have been well characterised.[1–4] Diabetes and other diseases that affect small vessels (hypertension, collagen vascular diseases, and chemotherapy), possibly increase the risk of radiation induced vasculopathy. However no study has proved this.[2–4] We reviewed retrospectively 469 uveal melanoma patients all treated with either ^{125}I brachytherapy or helium ion irradiation and compared both visual outcome and complications in diabetic and non-diabetic patients

All patients were examined in the Ocular

Oncology Unit, University of California, San Francisco. Retrospective chart review identified 20 diabetics (4·3%). All had both fundus photography and fluorescein angiography. Three patients were insulin dependent, 11 were on oral hypoglycaemics, and six used diet management of their diabetes. Prior to radiation three patients had proliferative retinopathy, four background, and 13 had no diabetic retinal disease on either ophthalmoscopy or fluorescein angiography. Two patients with proliferative retinopathy were treated with panretinal photocoagulation, one before and one after treatment. Any patient, diabetic and non-diabetic, developing significant proliferative retinopathy and/or rubeosis following irradiation was treated with panretinal photocoagulation. Tumour characteristics (Table 1) were similar in both diabetic and non-diabetic subjects; tumours in diabetics were located slightly more distant from fovea and nerve.

Table 1 Characteristics of tumours

Variable	*Diabetic*	*Non-diabetic*
Greatest base diameter	11·3 (3·2)	10·8 (3·9)
Shortest base diameter	9·7 (2·6)	9·0 (3·1)
Height	5·9 (2·1)	6·3 (2·6)
Distance to optic nerve	5·6 (4·5)	4·9 (3·8)
Distance to fovea	5·7 (4·9)	4·6 (4·0)
Neovascular glaucoma	25%	21%
Optic neuropathy	5%	12%
Radiation maculopathy	20%	12%

Standard deviations are in parentheses

The incidence of complications (Table 1) was higher in diabetics for neovascular glaucoma and radiation maculopathy, but lower for radiation optic neuropathy No significant difference was found for these three variables on the Cox regression model analysis ($p>0·05$). Covariates in the analysis were: tumour size and distance from the fovea and nerve, radiation type and dose, age, diabetes status, and presence or absence of hypertension. For those patients who lost vision, the mean time to visual acuity loss (two or more Snellen lines) was the same for diabetics and non-diabetics, 8·1 months. No significant difference was found for ultimate visual outcome. No significant correlation was found between pretreatment severity of diabetic retinal disease, complications, and visual outcome.

Anecdotal reports in the literature suggest that the diabetic eye is more likely to develop radiation morbidity.[2-4] Our review suggests that the difference in response is probably more subtle than previously thought. Because the number of diabetics in our study is small and incidence of complications low, the probability of detecting correctly a difference in response of the diabetic eye at the $p<0·05$ level is about one in five. Therefore our analysis may have missed identifying increased morbidity in diabetics. A definitive statement on diabetic radiation morbidity awaits additional data.

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Hyperopic shift and the use of masking agents in excimer laser superficial keratectomy

SIR,—I read with interest the articles on excimer laser treatment of superficial corneal disorders by Gartry *et al*[1] and Sher *et al*,[2] both of which attracted an editorial. I would like to comment on two aspects on this type of treatment both of which are, I believe, related to the use of masking agents (surface modulator fluids[2]).

Firstly in addition to the four potential mechanisms postulated to be responsible for the observed hyperopic shift in some patients[1] three further mechanisms are probably in play: (1) with multi-zone ablation using a 4 mm ablation diameter[1] it is almost impossible not to expose the axial cornea to more pulses of ablation than the more peripheral parts of the cornea (Fig 1a). It follows that a relative depression or flattening of the axial cornea would be created – a myopic correction is therefore cut (Fig 1b). A similar mechanism applies to the 'smoothing' technique used in the early cases of site 1 in the American report. It is conceivable that both regular and irregular astigmatism could be created in the same way.

(2) With single zone on-axis ablation, 1% hydroxypropylmethylcellulose (HPMC) creeps up the wall of the circular well created by repeated on-axis ablation (Fig 2a). Gartry *et al* commented that this surface tension effect may be minimised by wiping the walls with a cellulose sponge. These sponges were thought to be suboptimal in their absorptive properties when used in conjunction with 1% HPMC.[1] Capillarity has the effect of forming a relatively concave meniscus (Fig 2a), and it may be this relative concavity which becomes translated onto the ablated zone (Fig 2b), causing a hyperopic shift.

How can we test whether the latter hypothesis is true? There are two ways. (a) As the diameter of ablation is decreased the effect of the concavity will become more pronounced. The reverse will apply to a larger diameter of ablation. It follows that there should be less hyperopic shift with larger discs of ablation (Fig 3). (b) If on-axis single zone ablation is performed on normal clear cornea without the use of any form of masking agent there should be no hyperopic shift (see also epithelial hyperplasia below). The refractive result of this could be compared with a similar ablation with the use of HPMC.

(3) A third potential mechanism relates to the possibility of epithelial hyperplasia within the ablation zone especially adjacent to the wall of the well. A relative concavity can thus be created decreasing the refractive power of the cornea.

Sher *et al* also noted the phenomenon of hyperopic shift and compensated for it by preprogramming the laser to cut a secondary hyperopic correction ('combined' cut).[2] It would be of interest to know whether the refractive results quoted in each paper were obtained by retinoscopy, autorefraction, or subjective refraction, and whether there was any keratometric correlation.

Secondly it is intriguing to note that the two groups have come to opposite conclusions regarding the effectiveness of masking agents in creating an optically smooth surface. Gartry *et al* have unequivocally shown that it is possible to produce an optically smooth surface with the help of 1% HPMC. It was also pointed out that 2% HPMC and polyvinyl alcohol (PVA) were less suitable agents as they were too viscous,[1] thus the 2·5% methylcellulose used by Sher *et al* was clearly too thick. Furthermore Sher's results were also complicated by the use of an effluent fan causing ripples on the surface of the masking agent.[2] The ripples would in turn be etched onto the anterior surface of the cornea causing irregularities. Is an extraction fan necessary?

There are two theoretical advantages of using a fan. Firstly debris created by the ablation process would not be redeposited onto the cornea causing uneven ablation. Secondly both the surgeon and patient would be protected from the 'smoke' created by the ablative process. We do not know the nature of the airborne particles produced by ablating HPMC

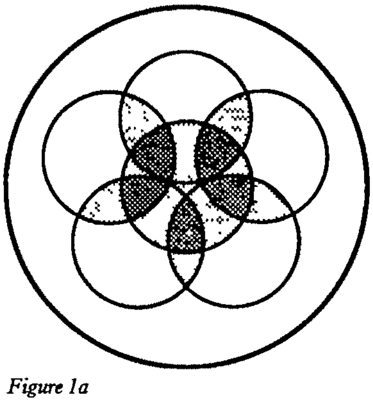

Figure 1a

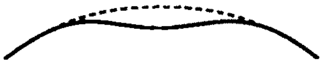

Figure 1b

Figure 1 Multiple ablation zones inevitably remove more corneal tissue axially (a). Profile of the cornea (b) thus created.

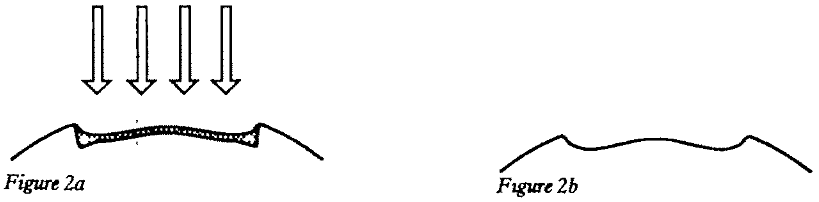

Figure 2a *Figure 2b*

Figure 2 Cross-sectional diagram of the cornea (a) showing how surface tension could create a relatively concave meniscus. (b) With repeated ablation, this profile is etched onto the cornea.

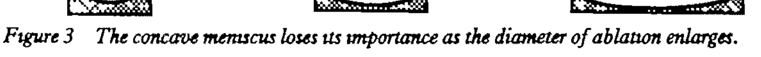

Figure 3 The concave meniscus loses its importance as the diameter of ablation enlarges.

and biological tissues[1] and more research is needed. When a masking agent is used, a fan causing ripples on the surface is undoubtedly undesirable.

Masking agents provide the key to producing a regular surface from an irregular one and must not be dismissed. Gartry *et al* obtained superior results because great care was taken continuously to refill and uniformly to redistribute the masking agent over the ablated area and constantly to monitor the changes in tissue fluorescence.[1] This is a surgical art rather than 'worshipping at the altar of high technology.'[3]

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1 Gartry D. Kerr Muir M, Marshall J. Excimer laser treatment of corneal surface pathology a laboratory and clinical study. *Br J Ophthalmol* 1991, 75: 258–69.
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Reply

SIR,—Following on the interesting comments made by Dr Liu in his letter we reported[1] that superficial keratectomy with the excimer laser results in a hyperopic shift of 2·85 dioptres on average in our series. This was an unexpected finding since we had assumed that photoablation of an even layer of tissue across the entire cross-section of the beam (4 mm in diameter in most cases) would produce no change in corneal curvature. This is in contrast to the planned change in corneal curvature attempted when a motorised iris diaphragm is used during photorefractive keratectomy.

We put forward four possible mechanisms to explain this phenomenon. (1) The distribution of calcium within the band keratopathy might mask the beam allowing greater ablation of tissue centrally. (2) A centrifugal contraction of the lamellae at the ablated surface. (3) Shielding of the periphery of the beam by debris ejected from the surface. (4) Increased obliquity of incident radiation at the edge of the beam (due to the curvature of the cornea) resulting in slightly less photoablation in the periphery of the ablation zone.

We described the treatment of two main categories of anterior corneal pathology – namely rough surfaces and smooth surfaces. The background and principles of superficial keratectomy with the excimer laser to smooth a rough surface were documented in detail and in particular the importance of masking areas of stroma between surface peaks to avoid reproducing the surface irregularity deeper into the cornea. We found 1% methyl cellulose optimal for this purpose. When treating the second category (for example smooth band keratopathy) since we started with a smooth surface it was unnecessary to apply any masking agent. As we explained in our paper in general the eyes with the best visual potential fell into this latter category and it was in these cases that subjective refraction revealed a hyperopic shift (cases 18, 19, 21, 22 and 23).

Dr Liu suggests that when using overlapping ablation zones more tissue will be removed from the central cornea due to intersection of treated areas. This is not the explanation since we found considerable hyperopic shift in patients treated with a single axial zone (for example cases 22 and 23). In addition, in those patients with good visual potential treated with multiple zones a 4 mm central zone was usually cleared first followed by continuous areas with minimal overlap. He also states that 'it is conceivable that both regular and irregular astigmatism could be created in the same way.' We agree with this of course since we documented the effect in case 19. As stated in our paper it was this potential for irregular astigmatism when using multiple continuous zones that led us to conclude that where good visual potential exists a single central zone is the most effective treatment method.

Dr Liu's second suggestion to explain the hyperopic shift relates to the use of methyl cellulose and since this was only employed (as stated) in cases with rough corneal surfaces (where the aim was smoothing rather than glare reduction and improvement in acuity) this cannot provide a basis for the effect.

The third mechanism proposed however – that of epithelial hyperplasia – warrants further consideration. We have found that regenerating epithelium accounts for a large part of the regression in refraction occurring in our photorefractive keratectomy series. We have hypothesised that epithelial hyperplasia over the ablated zone accounts for the first part of an asymptotic regression towards a plateau with stromal remodelling providing the basis for subsequent lesser change. It is difficult to envisage that entirely the reverse could occur when treating smooth band keratopathy. We also suggest that any 'relative concavity' due to hyperplasia at the edge of the ablated zone would be minimal since it is necessary only to ablate between 10 and 15 µm of stroma (virtually only Bowman's layer) to clear smooth band keratopathy and this is a shallow ablation compared with the thickness of the overlying regenerated epithelium.

Of the four mechanisms proposed in our paper to explain the hyperopic shift we favour centrifugal contraction of lamellae resulting in a flattening of central cornea. This concept will be clarified further and evidence in its support provided when we report our photorefractive keratectomy series.

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1 Gartry D, Kerr Muir M, Marshall J. Excimer laser treatment of corneal surface pathology: a laboratory and clinical study. *Br J Ophthalmol* 1991; 75: 258–69.

Treatable blindness in temporal arteritis

SIR,—I read with interest the recently reported case.[1] The author reported dramatic visual recovery in the second episode of anterior ischaemic optic neuropathy (AION) when pulsed IV steroid therapy (methylprednisolone, 500 mg daily for 2 days) was used, and recommends this treatment for visual loss due to AION caused by giant cell arteritis (GCA) despite its attendant mortality and morbidity.[2] Clearly this recommendation can only be accepted if a clear benefit of this treatment can be demonstrated over the more conventional steroid treatment of 80–100 mg prednisolone orally.[3] I would suggest there is no evidence of such benefit particularly as, during the first episode of AION this patient suffered, there was an equally impressive recovery of vision on 60 mg of prednisolone orally daily. It seems reasonable to suppose that this may have again occurred had conventional therapy been used.

As the author points out when there is severe visual loss from AION secondary to GCA marked improvement is rare although several other cases of substantial visual improvement using 80 mg prednisolone orally daily are reported.[3,4]

Pulsed IV steroids are recommended by the standard reference textbook of ocular pharmacology which states 'with acute visual loss of less than 36 hours duration significant visual improvement may be obtained with 'pulsed' steroid therapy using 1 gm of methylprednisolone intravenously every 12 hours for 5 days.'[5]

Only two case reports are cited as evidence to support this statement, and both are discussed by Mr Diamond. However neither is particularly persuasive.

In the case reported by Model[6] vision had at no stage been formally tested. In addition prior treatment had been inadequate and of short duration (a single intravenous dose of 100 mg of hydrocortisone and no more than 20 mg of methylprednisolone orally (10 mg four times daily for 12 h). It is therefore uncertain what the degree of alteration in vision was and whether pulsed IV steroid was essential to accomplish it.

In the other case[7] vision in the eye for which pulsed IV steroids were given was 20/70 before the patient was referred for a second opinion. When assessed immediately prior to pulsed IV steroids, vision was 20/40 ('slowly'), with an inferior altitudinal scotoma to I4e on Goldmann perimetry and ability to recognise only seven of 15 colour vision plates. Following pulsed IV steroids the field loss recovered and visual acuity improved to 20/25. No details are given of how quickly she read or of colour appreciation. The authors claim to have 'restored vision' seems to overstate the case. More accurately they seemed to have arrested moderate fluctuations of vision. It is worth emphasising that, judging from the recorded changes in visual acuity, the majority of improvement (20/70 to 20/40) had occurred before pulsed IV treatment was used (visual acuity improved from 20/40 to 20/25 following this treatment) and it may be argued that recovery was inevitable in any event.

Recovery of vision on AION due to GCA is by no means invariable with pulsed IV steroids and progressive visual loss during therapy has been reported.[8]

Although appropriateness of corticosteroids in the treatment of GCA with starting doses of 80-100 mg orally is well established,[3] it is apparent that the evidence to support the use of pulsed IV treatment in order to restore visual function lost from AION due to GCA is deficient. In view of the potential for adverse effects (in the age group most susceptible to adverse effects of steroid) formal critical evaluation of any therapeutic efficacy is required before recommendations for use of this treatment can be accepted.

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8 Slain ML Margolis AJ Progressive anterior ischaemic optic neuropathy due to giant cell arteritis despite high dose intravenous corticosteroids *Arch Ophthalmol* 1988; 106: 1167

Reply

SIR,—I agree that the possible adverse effects of this drug must be carefully weighed against the potential benefits and moreover that the efficacy of the drug requires a full critical evaluation.

However until this evidence is forthcoming I consider that methylprednisolone does have a role in treatment of certain cases of temporal arteritis.

While methylprednisolone is a commonly used drug the number of serious side effects reported is low. Conversely there is a significant morbidity and mortality consequent upon bilateral visual loss in the elderly.

Thus I consider use of methylprednisolone is justified when blindness is threatened; for example, in patients who develop second-eye symptoms when already taking a significant dose of oral prednisolone or for patients who delay presentation until after the second eye has failed.

Total blindness is a catastrophic complication of temporal arteritis. The potential prevention of this outcome would seem to justify utilisation of a relatively safe if unproved therapy.

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BOOK REVIEWS

Converting to Phacoemulsification: A Manual for the Surgeon in Transition. 2nd edn. By Paul S Koch. Pp 84. £24.00. Wiley: Chichester, West Sussex, 1988.

I was particularly delighted to review this book because when I was in the early stages of converting to phacoemulsification for the management of cataract patients this was a book I purchased and consumed both with pleasure and benefit. It is a slim volume designed specifically to encourage and assist the surgeon undergoing the process of converting to phacoemulsification. This process can be uncomfortable and painful from time to time and encouragement and assistance are both very welcome. The author's style is distinctly chatty but is always very much to the point.

In its 12 short chapters it covers every aspect of the procedure and the important points are illustrated by simple line drawings. No important technical point is omitted I should, however, point out that in my experience no textbook can replace the value of an instructional course when it comes to phacoemulsification. This is a subtle surgical procedure requiring skill and care and it is much less comfortable to discover its pitfalls by unguided surgical experience rather than to have been forewarned and forearmed against them. The greatest strength of this little book is its encouraging tone and the author's unwavering belief that what he has to say is in both the surgeon's and the patient's best interests. If it has a weakness it is that it does not take account of some of the more recent developments in cataract management, particularly capsulorhexis and phacoemulsification within the capsular bag. These are, however, techniques which a converting cataract surgeon does need to acquire quite early. I hope that future editions of this volume will cover this omission.

A D McG STEELE

Sodium Hyaluronate in Anterior and Posterior Segment Surgery. By R G Michels, W J Stark, M Sirpe, Pp 131. US$ 35. Liviana Press: Via L Dottesio, 1–35138 Padova, Italy, 1989.

This book is dedicated to the use of sodium hyaluronate in all aspects of intraocular viscosurgery. It is edited by a team of well known American and Italian ophthalmologists, and the manufacturers of the product appear to have played a prominent part in the production of the book.

The text is relatively short but clear. The introductory section deals with the chemistry, physics, and physiological properties of sodium hyaluronate. This is followed by four chapters about the clinical applications of this undoubtedly useful substance. Having discussed its use in surgery of the anterior segment and glaucoma, the editors devote the largest section of the text (and the largest volumes of sodium hyaluronate) to surgery of the posterior segment. There are many colour paintings which make the procedures look deceptively simple and free of complications.

All in all this is a beautifully illustrated book which is easy to read, but unless there is a sudden change in the price of sodium hyaluronate it is likely to be limited value to most readers in Britain.

Z GREGOR

Noninvasive Diagnostic Techniques in Ophthalmology. Edited by Barry R Masters. Pp 650. Dm 298.00. Springer-Verlag: Heidelberg, 1990.

This book is an excellent production comprising more than 600 pages and 32 chapters on up-to-date methods of investigation in our specialty. The range of topics covered is wide, varying from magnetic resonance imaging through holographic contour analysis of the cornea to scanning laser and image analysis of infrared choroidal angiography.

Many of the contributors are scientists and not clinical ophthalmologists but their chapters are full of interest though several admit the clinical application of their expertise awaits analysis. Most chapters end with some paragraphs on the present clinical application of the method described and also look into the future regarding potential developments The references provided are full and frequent suggestions for further reading are included. Many of these references are in non-ophthalmic journals and monographs and the reader cannot fail to recognise the tremendous contributions being made to the advancement of knowledge by scientific workers in our field

The whole book is fascinating and of immense value to those in the clinical field who may have access to the expensive research instrumentation and the expert knowledge of the relatively few people who know how to manipulate the software and hardware required.

I have the feeling though that, rather like encyclopaedias, the information will rapidly become dated as new devices are developed. I wonder if the editor might consider producing an update at periodic intervals to permit this current publication to remain as the authoritative textbook of noninvasive techniques as cleverly defined in the foreword.

I will enjoy having access to this beautifully presented book with its fascinating photographs and hopefully the possibility will arise of the clinical application becoming available to an increasing number of workers as time and finance become available.

WILLIAM M DOIG

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (Mastercard, Visa, or American Express), stating card number, expiry date, and full name.

NOTES

International Society of Ocular Trauma

The Society will hold its 2nd International Symposium on Ocular Trauma on 2–5 April 1992 in Geneva, Switzerland. Further details from: The Secretariat, 2nd International Symposium on Ocular Trauma, c/o Kuoni Travel Ltd, 7 Rue de Berne, CH-1211 Geneva 1, Switzerland (tel: 41 22 732 0888; fax 41 22 731 5078; tlx: 412831)

Welsh Cataract Congress 1992

The Welsh Cataract Congress will be held on 10–12 September 1992. Further information from: Eula Mae Childs, Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin (NC200), Houston, TX 77030, USA. Tel: 713–798–5941.

Biomedical Optics '92

The International Society for Optical Engineering will hold a symposium under this title on 19–24 January, 1992 at Los Angeles Airport Hilton Hotel. Details from the Society at PO Box 10, Bellingham, Washington 98227–0010, USA.

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Intraocular involvement with subretinal pigment epithelium infiltrates by mycosis fungoides

Barbara C Erny, Peter R Egbert, Irene M Peat, K Shorrock, A Ralph Rosenthal

CORRECTION

This article appeared in the November 1991 issue of British Journal of Ophthalmology. Unfortunately we printed the incorrect colour pictures on page 698. This insert is the correct version of that article.

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British Journal of Ophthalmology, 1991, 75, 698–701

Intraocular involvement with subretinal pigment epithelium infiltrates by mycosis fungoides

Barbara C Erny, Peter R Egbert, Irene M Peat, K Shorrock, A Ralph Rosenthal

Abstract

We report a case of intraocular mycosis fungoides in a 48-year-old man. The patient presented with decreased visual acuity, white subretinal lesions, and vitritis. Post-mortem histopathology revealed malignant T cell infiltrates consistent with mycosis fungoides in the retina, vitreous, and between the retinal pigment epithelium (RPE) and Bruch's membrane. Focal atrophy of the RPE, along with the sub-RPE infiltrates, correlated with the clinically visible fundus lesions.

Mycosis fungoides is a cutaneous T cell lymphoma, which can progress to generalised disease.[1] It commonly presents with a long phase of 'premycotic' skin lesions. These progress to patches on the skin, which may or may not become plaques, and eventually tumours.[2] The clinical course of skin involvement varies from chronic to rapidly progressive, and is unpredictable.[3] Systemic involvement is late in the course of the disease, and usually involves the lymph nodes, liver, spleen, and/or central nervous system.[4] Because the majority of patients develop the disease between the ages of 40 and 60, many of them die of unrelated causes before the disease becomes widespread.

Eyelid and conjunctival involvement is not unusual in the course of mycosis fungoides.[5] Other external ocular involvement has been reported, including cornea,[6] caruncle,[7] sclera,[6] and orbit.[8] Intraocular lesions are rare, and only a few individual cases have been reported. Only one of the previous reports records both the clinical and pathological appearance of intraocular mycosis fungoides.[9]

We present here a patient followed up closely for an ocular disease that resembled fungal endophthalmitis but was histologically proved to be mycosis fungoides.

Case report

The patient was a 48–year-old white man known to have had mycosis fungoides for 30 years. He had disseminated skin lesions for which he received topical steroids, psoralen and ultraviolet light (PUVA), superficial *x* ray therapy, and in 1989 intermittent oral chlorambucil (Leukerad). In 1983 he had undergone surgery for a subarachnoid haemorrhage.

On 1 November 1989 the patient complained of blurring of vision mainly in the left eye. Ophthalmic examination revealed bilateral disc swelling and small white lesions in the fundus (Figs 1A, B. The disc swelling resolved spontaneously. Four weeks later his vision dropped to 6/12 in the right eye and counting fingers in the left. The left eye showed anterior uveitis, and severe vitritis with active retinitis in the posterior pole (Fig 2). The left eye had also developed a conjunctival perilimbal nodular yellow infiltrate (Fig 3). A presumed diagnosis of candida chorioretinitis was made, and the patient was treated with intravitreal amphotericin and oral ketoconazole. Cultures and stains of vitreous biopsies were negative, and oral ketocanazole was continued. By 5 December the right eye also developed a small white lesion in the macula (Fig 4), a limbal lesion, and conjunctival infiltrates.

At the same time the patient was admitted to hospital for control of pain and a newly discovered left sided abdominal mass. He died on 21 December 1989, with a diagnosis of mycosis fungoides and widespread lymphoma.

POST MORTEM FINDINGS

The body was covered with numerous crusting skin lesions up to 2 cm in diameter. There was evidence of extensive involvement of the lymph nodes by lymphoma, which also appeared to be infiltrating retroperitoneal tissues.

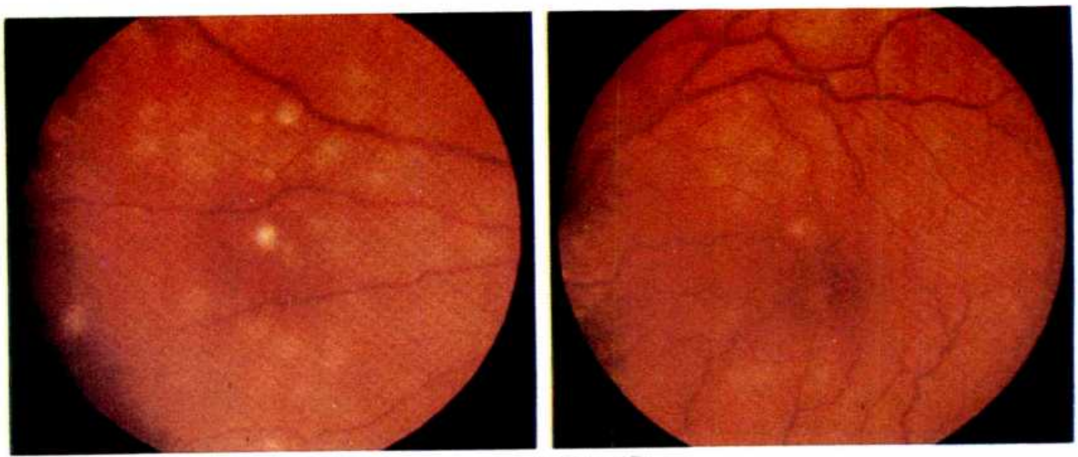

Figure 1A *Figure 1B*

Figure 1 Fundus photographs of the patient with APMPPE on the day of presentation. A: Right eye. B: Left eye.

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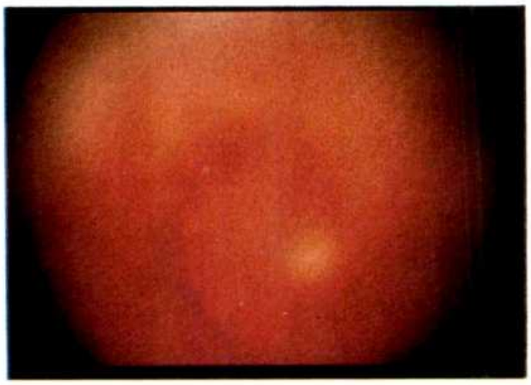

Figure 2 Fundus, left eye. Four weeks after the retinal lesions were first observed the patient developed vitritis with active retinitis.

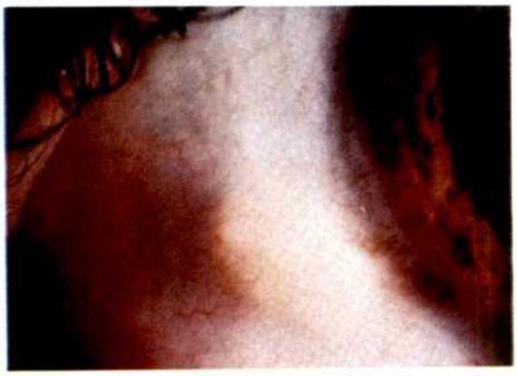

Figure 3 Left eye. This nodular perilimbal conjunctival infiltrate was noted four weeks after the patient's initial eye examination.

Microscopically the dermis displayed a diffuse infiltrate of small lymphocytes plus occasional larger cells with bizarre hyperchromatic nuclei. In some areas there was infiltration into the epidermis, though discrete microabcesses were not identified. There was heavy lymphoid infiltrates within the cortex of the left kidney which extended to the surface and infiltrated perinephric tissues. A similar lymphoid infiltrate was seen in the myocardium and testis. Lymph nodes from the periaortic region also showed effacement of the architecture by a similar infiltrate, which extended widely into the surrounding fatty tissue. Immunocytochemical markers indicated that the infiltrate was predominantly composed of T lymphocytes.

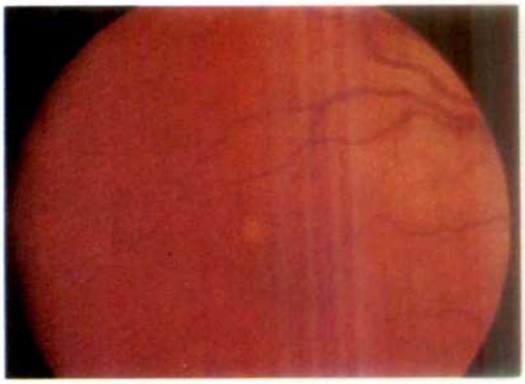

Figure 4 Fundus, right eye. Small white subretinal lesion in the macula.

The histological appearances were consistent with a T cell lymphoma arising in mycosis fungoides and leading to diffuse visceral infiltration.

OCULAR HISTOPATHOLOGY

Both eyes showed similar findings, these being more pronounced in the left eye. Anteriorly the eyes were normal. The striking feature in the posterior segment was the presence of abnormal lymphocytes, which were consistent with mycosis fungoides, between Bruch's membrane and the retinal pigment epithelium (RPE). The cells had scanty cytoplasm and large pleomorphic nuclei with convoluted borders (Fig 5). The infiltrate formed a diffuse layer, 1 to 15 cells thick, under the equatorial and peripheral RPE, and also extended a short distance under the pars plana epithelium. The thickness of this infiltrate varied throughout the specimen and often changed abruptly from sparse to dense. The overlying RPE showed variable focal degeneration and atrophy (Fig 6). The retina contained loose focal infiltrates of lymphomatous cells in the nerve fibre layer and ganglion cell layer, particularly round the retinal vessels (Fig 7). The outer retinal layers were normal. The choroid had a mild diffuse infiltrate of similar abnormal lymphocytes (Fig 8). Lymphomatous cells also infiltrated the small amount of vitreous base which remained after the vitrectomy (Fig 9). The ciliary body, iris, and episclera contained a slight lymphocytic infiltrate but no large lymphoma-like cells.

The optic nerve and conjunctiva were not available for examination.

IMMUNOHISTOPATHOLOGY

The isolated cell population found between the RPE and Bruch's membrane was studied further by immunoperoxidase stains on paraffin sections. There was a positive reaction for the leucocyte common antigen (PD7) and two pan-T cell markers (L60, A6). The pan-B marker (L26) was non-reactive, which would be unusual in a benign lymphoid infiltrate. Therefore the find-

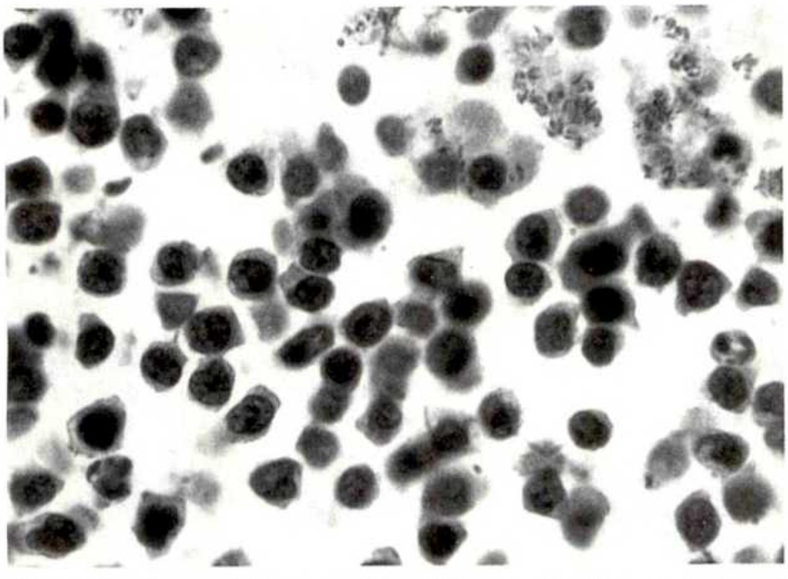

Figure 5 Lymphomatous infiltrate beneath the RPE contains cells with scanty cytoplasm and large pleomorphic nuclei with convoluted borders, consistent with mycosis fungoides. (Haematoxylin and eosin, ×400.)

ings indicated exclusive T cell proliferation consistent with involvement of the eye by micosis fungoides.

Discussion

Intraocular involvement of mycosis fungoides has been rarely reported. Gartner[10] reported the first known case, in which the choroid was infiltrated with neoplastic cells. Hogan[11] presented a case in which the uvea was infiltrated with neoplastic cells and the optic nerve had tumour anterior to the lamina, which extended to the adjacent retina. Keltner *et al*[9] described a patient with involvement of the central nervous system and eyes in whom at necropsy mycosis fungoides cells were found in the retina, optic disc, and vitreous. Foerster[12] presented a case and described the pathological finding of neoplastic cells forming a diffuse layer beneath the RPE, as seen in the present case. Intraocular involvement has been noted only in the end stage of the disease in all of these cases: from 17 days[11] to one year before death.[12] In our patient the eye involvement was discovered seven weeks before his death.

In this paper we present a case of mycosis fungoides with clinical and pathological correlates of the intraocular involvement, which most strikingly includes infiltrates between the RPE and Bruch's membrane. In our sections it appears that cells have arrived in the sub-RPE potential space by crossing Bruch's membrane from the choroid. Barr *et al*[13] reported two cases of similar lesions in large cell lymphoma. This finding suggests that lymphocytes from various lymphomas may have a predilection to accumulate in the sub-RPE space. The retinal perivascular infiltrates and vitreous metastases are similar to those reported by Keltner *et al*[9] Metastases to the retina characterised pathologically by collarettes of tumour cells surrounding retinal vessels, evidently occur by haematogenous spread, as has also been reported in leukaemia.[14]

The lesions in our patient clinically mimicked candida chorioretinitis, with white retinal spots and overlying vitreous haze. However, the histopathology shows that the white spots are focal atrophy of the RPE and accumulation of lymphomatous cells beneath the RPE. Patients with mycosis fungoides are not particularly susceptible to candida infection unless they are immunocompromised from chemotherapy, or have other risk factors.[15]

Ophthalmologists asked to see patients with extracutaneous mycosis fungoides need to consider strongly the possibility of intraocular malignancy. Radiotherapy has successfully treated an orbit infiltrated by mycosis fungoides.[16] There has also been a report of focal radiotherapy to an involved caruncle with complete resolution.[7] Perhaps focal radiation to the retina and choroid could be given in an attempt to preserve vision in patients with intraocular mycosis fungoides.

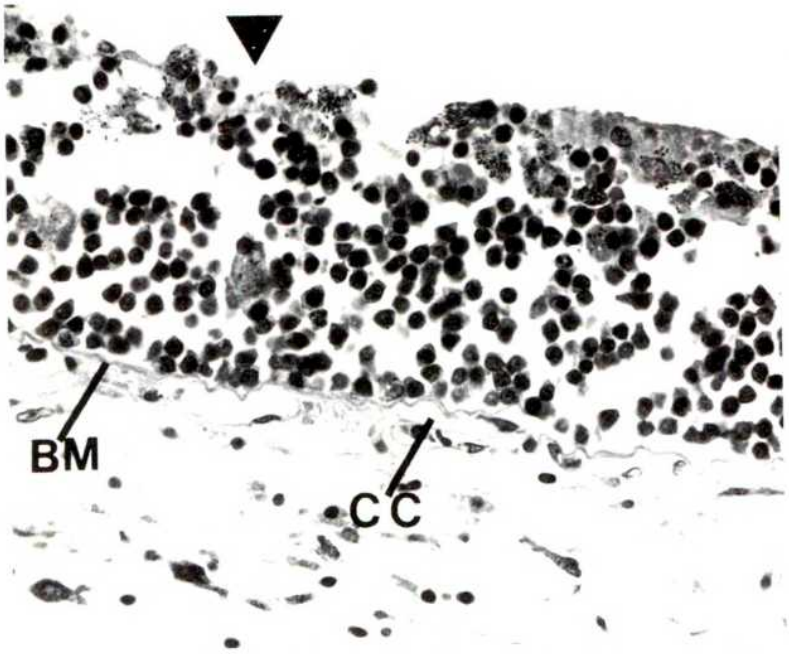

Figure 6 The infiltrate forms a diffuse layer of lymphomatous cells under the RPE. In this area the infiltrate is thick. The overlying RPE exhibits variable focal degeneration and atrophy (arrowhead). Bruch's membrane (BM) is intact, and the choriocapillaris (CC) is normal. (Haematoxylin and eosin, ×200.)

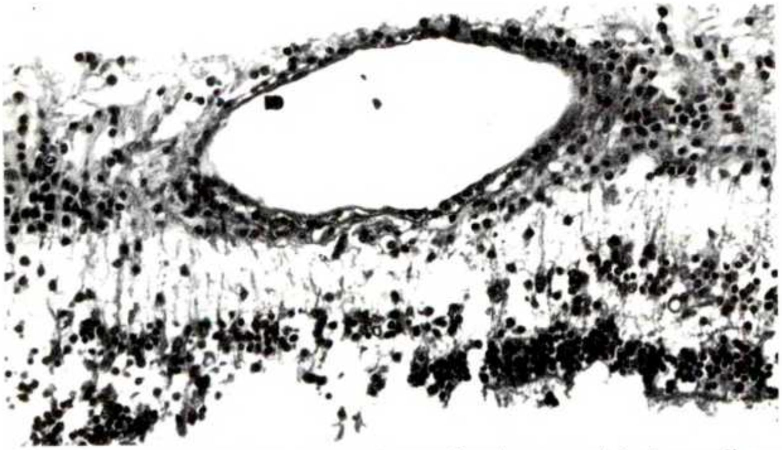

Figure 7 The retina contains loose focal infiltrates of lymphomatous cells in the nerve fibre layer and ganglion cell layer, here shown concentrated around a retinal vessel. (Haematoxylin and eosin, ×200.)

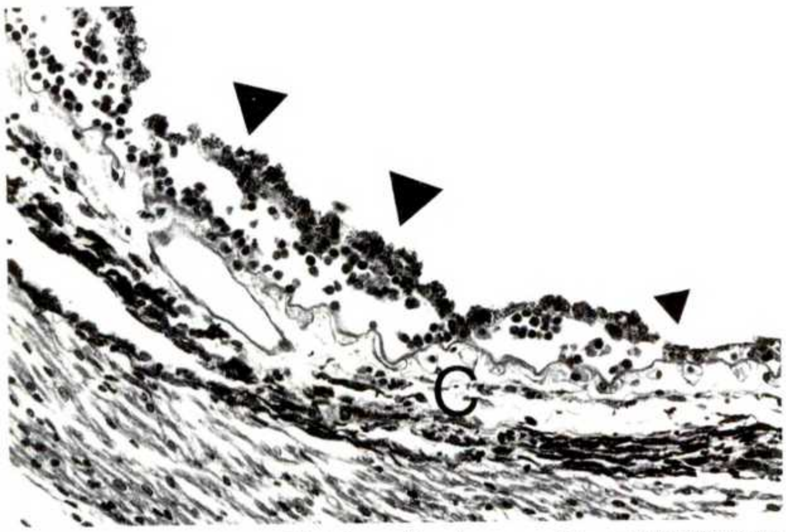

Figure 8 In this area there is a thin infiltrate of lymphomatous cells beneath the RPE (large arrowheads) and beneath the epithelium of the pars plana (small arrowhead). The choroid (C) contains a scanty lymphomatous infiltrate. (Haematoxylin and eosin, × = 100.)

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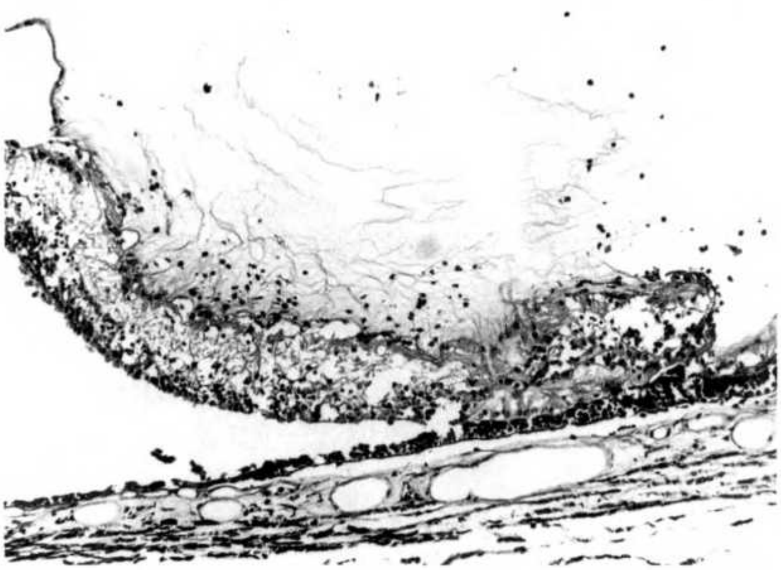

Figure 9 Lymphomatous cells are seen infiltrating the remaining vitreous at the vitreous base adjacent to the ora serrata. (Haematoxylin and eosin, ×40.)

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Choroidal vasculitis in acute posterior multifocal placoid pigment epitheliopathy

Richard F Spaide, Lawrence A Yannuzzi, Jason Slakter

CORRECTION

This article appeared in the November 1991 issue of British Journal of Ophthalmology. Unfortunately we printed the incorrect colour pictures on page 685. This insert is the correct version of that article.

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Choroidal vasculitis in acute posterior multifocal placoid pigment epitheliopathy

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Abstract

A 24-year-old Caucasian female presented with acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and associated infiltration round some of the larger choroidal blood vessels. This infiltration dissipated as the patient's clinical condition improved and did not induce any permanent alteration of the overlying retinal pigment epithelium. We suggest that the infiltration round the choroidal vessels was due to a choroidal vasculitis. The finding of choroidal inflammation in this case lends support to the hypothesis that choroidal vasculitis is an underlying pathological process in APMPPE.

In 1968 Gass[1] described three young women who developed a rapid, but transient, loss of visual acuity associated with multiple yellow-white placoid lesions at the level of the retinal pigment epithelium (RPE). Although the presence of choroidal involvement could not be ruled out, the disorder was presumed to involve primarily the RPE and was named with the descriptive term, acute posterior multifocal placoid pigment epitheliopathy (APMPPE).[1] The concept that a choroidal vasculopathy played a part in the pathogenesis of APMPPE was the first made by Van Buskirk and associates.[2] Deutman and associates[3] suggested that an acute inflammation of the choriocapillaris might be the initial incident in APMPPE and the RPE changes were a subsequent manifestation. Several systemic findings associated with APMPPE involve a vasculitis – retinal vasculitis,[4-7] cerebral vasculitis,[8,9] and erythema nodosum[2,3,6] – which seems to support this hypothesis.

Direct evidence of choroidal vascular inflammation has remained elusive in APMPPE because the placoid lesions, as well as the melanin in the RPE and the melanocytes of the choroid, usually block visualisation of the choroidal vessels. We recently examined a young woman with APMPPE who had clinically discernible infiltrates of some of her peripheral choroidal vessels.

Case report

A previously healthy 24-year-old fair-skinned, red-haired woman was referred for ophthalmological examination because of a four-day history of decreased vision in the right eye associated with severe headaches. She had a visual acuity of 20/60 in the right eye and 20/20 in the left. Fundus examination revealed multiple yellow-white placoid lesions at the level of the retinal pigment epithelium in both eyes (Figs 1A, B). The lesions were hypofluorescent in the early stages of the fluorescein angiogram but showed late staining. Two weeks after presentation the headaches stopped, but her visual acuity declined to counting fingers at 4 feet (120 cm) in the right eye and 20/400 in the left, secondary to bilateral foveal lesions. Fluorescein angiography at this time showed larger choroidal vessels in the subacute lesions (Fig 2), very slow filling of the choriocapillaris, and late staining of the lesions. There were no placoid lesions anterior to the mid-periphery.

In the periphery of both eyes some of the choroidal vessels were surrounded with patchy, segmental yellowish infiltration (Figs 3A, B and 4A, B). Several of the more prominently involved vessels clearly led to the ampulla of the vortex veins; in other involved choroidal vessels the classification of artery or vein could not be made.

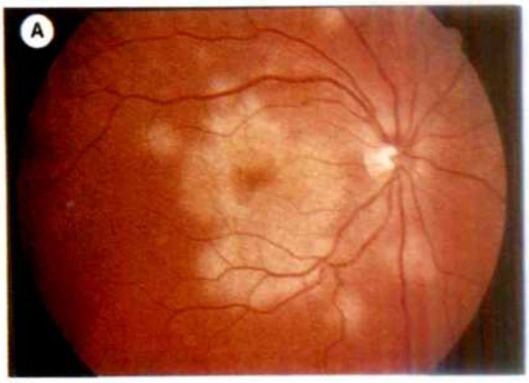

Figure 1A

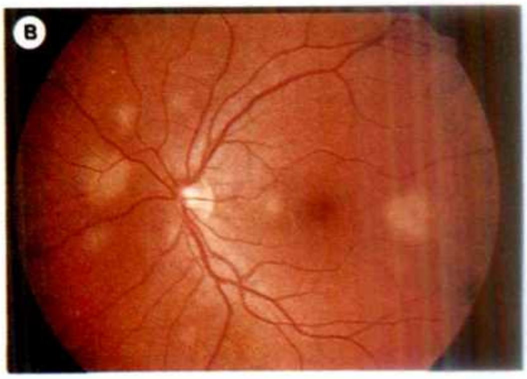

Figure 1B

Figure 1 Fundus, left eye. A Small circumscribed white subretinal lesions were seen throughout the mid periphery of the retina. B There was one lesion in the macula.

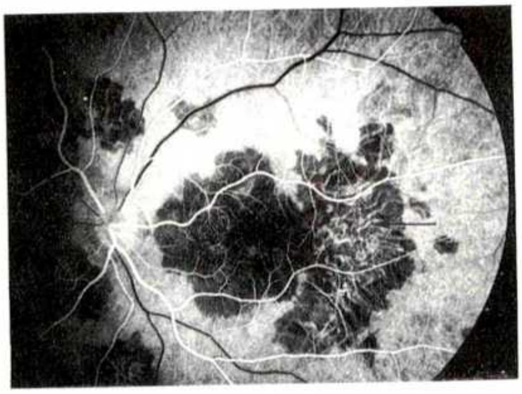

Figure 2 Early phase fluorescein angiogram of subacute lesions in the same patient two weeks after presentation. The subacute lesions were characterised by resolution of the dense placoid lesions, atrophy of the involved retinal pigment epithelium, and unveiling of the choroidal circulation. In such lesions the larger vessels could be seen during the early stages of the fluorescein angiogram, but the blush due to the filling of the choriocapillaris was not present.

The choroidal infiltration did not appear to involve the RPE by slit-lamp biomicroscopic examination with a three-mirror contact lens.

Over the next seven weeks both the placoid lesions and the peripheral choroidal vascular changes slowly resolved in parallel. Ten weeks after presentation the visual acuity was 20/40 in both eyes. The choroidal infiltrates had resolved in both eyes without detectable damage to the larger choroidal vessels or any discernible change of the overlying RPE.

During the course of her illness she was not noted to have any abnormalities of the external eye, anterior chamber, vitreous, or retinal vessels. Laboratory tests included a complete blood count with differential count, liver function tests, thyroid function tests, electrolytes, Lyme disease titres, and a chest roentgenogram. With the exception of a borderline low serum iron level, all tests gave normal results.

Discussion

Infiltration round retinal vessels commonly occurs in conditions that cause a retinal vasculitis. We suggest that the infiltration round the choroidal vessels in our case of APMPPE represents a choroidal vasculitis or an accumulation of the by-products of inflammation round the involved choroidal vessels. A total of six patients are mentioned in four previous reports concerning retinal vasculitis associated with APMPPE,[4-7] and in each instance the involved vessels were veins. In our patient several of the involved choroidal vessels could be identified as veins, but no identification could be made about other vessels.

While choroidal inflammatory disease has been implicated in the pathogenesis of APMPPE, clinical signs of choroidal vasculitis in the acute stages of the disease have not been described. Several factors probably contributed to our visualisation of the choroidal infiltrates in the periphery, but not in the posterior pole. In the mid and far peripheral fundus the RPE is more attenuated and the larger choroidal vessels lie closer to the RPE than in the posterior pole.[10] The clinical focus of the disease, as implied by the name, is in the posterior pole, where the placoid lesions obscure the underlying choroidal vessels.

Many reported cases of APMPPE have had the prodromal symptoms of headache, fever, malaise, and myalgia.[11-19] These symptoms were ascribed by the patients or the investigators to a cold, influenza, or other viral infection. It has been presumed that these prodromal infections, directly or indirectly, caused an inflammation of the choroidal vessels, with APMPPE as a consequence. Although antecedent viral infections frequently have been implicated as the cause of APMPPE, the evidence for this supposition is far from compelling. In only one case of APMPPE was a virus, adenovirus type 5, isolated,[20] but this patient developed evidence of the viral infection 19 days after being affected by APMPPE, raising the suspicion that this association may have been coincidental. Another case of APMPPE associated with acute nephritis had a positive immunofixation test for the virus of epidemic nephritis,[21] but there was no increase in the antibody titre during the course of the disease.

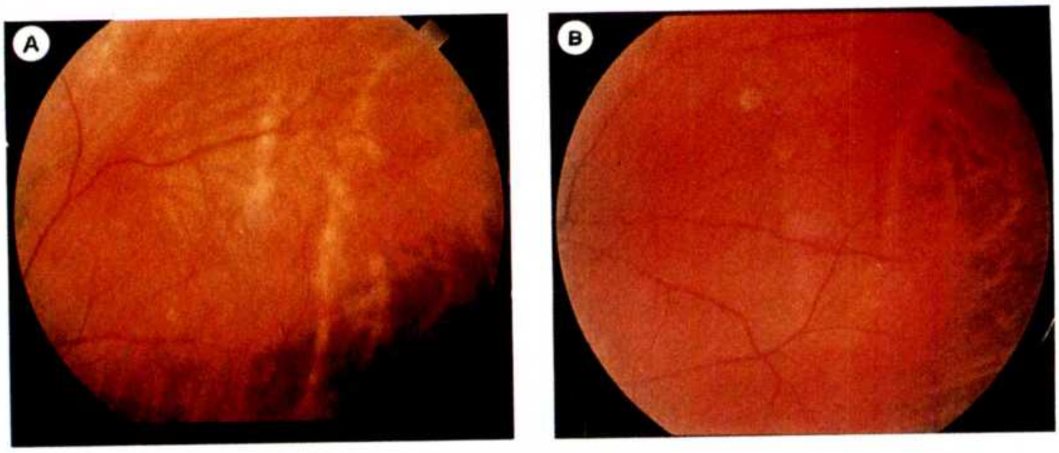

Figure 3A

Figure 3B

Figure 3 Choroidal inflammation in APMPPE. A: Infiltration round a choroidal vessel as seen three weeks after initial presentation. B: Disappearance of the choroidal inflammation 10 weeks after presentation, with no residual damage to the retinal pigment epithelium.

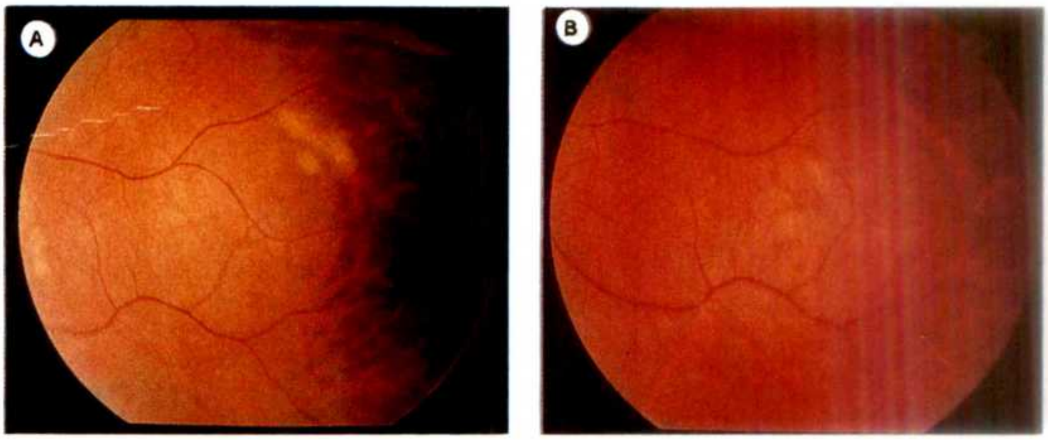

Figure 4A *Figure 4B*

Figure 4 Choroidal inflammation in APMPPE. A: A focal area of infiltration around a choroidal vessel as seen three weeks after presentation. B: Complete resolution 10 weeks after presentation with no damage to the pigment epithelium.

While non-specific symptoms such as headache, fever, malaise, and myalgia can be associated with a cold or viral condition, they also can occur as part of a vasculitic syndrome.[22] It is possible that in some cases the headache, fever and malaise are manifestations of a transitory systemic vasculitis, of which APMPPE is a part. This vasculitis could account for the observation of cerebral vasculitis, retinal vasculitis, erythema nodosum, and in our case choroidal vasculitis in APMPPE. Although the finding of choroidal vascular infiltration in this patient does not prove that choroidal vasculitis is a requisite for APMPPE, it does lend support to the hypothesis that choroidal vasculitis plays a part in its pathogenesis.

The authors recently examined a second consecutive case of APMPPE after this report was written. While the disease was active scattered infiltrates around the choroidal vessels were found and these infiltrates appeared similar to those described in this report. The infiltrates resolved as the posterior pole lesions regressed. There was no abnormality of the overlying retinal pigment epithelium after the resolution of the infiltration.

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BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

Prospects for day-case vitreoretinal surgery

In the United Kingdom management of patients undergoing eye surgery as outpatients or day-cases has, until recently, been largely restricted to minor extraocular procedures, while the use of local anaesthesia, even for inpatients, has been similarly limited. Ready availability of highly trained anaesthetic personnel and easy access to high quality inpatient facilities fostered by four decades of socialised medicine has encouraged British ophthalmologists to rely on general anaesthesia for a disproportionately large number of cases compared with their counterparts in other countries. While it can be argued that general anaesthesia is no barrier to the practice of day-case surgery most ophthalmic procedures lend themselves so well to the use of local anaesthesia that, in ophthalmology, the great majority of day-cases are performed under local anaesthesia.

In parts of the world with a lower standard of living shortages of trained personnel, drugs, and other medical facilities encourage surgical practices to utilise the minimum of resources for the maximum results, including rapid surgical turnover, optimum use of beds, and rapid return to the community for aftercare. In the more affluent capitalist societies the high costs of hospital care similarly discourage inpatient treatment.

Surgery under local anaesthesia administered by the surgeon not only reduces the need for other highly trained medical personnel during surgery but also the need for expensive hospital facilities pre- and postoperatively. The use of day-case surgery, usually carried out under local anaesthesia, is thus a logical outcome of market orientated medical care whether the patients are affluent but facilities expensive or resources scarce and the consumers impoverished.

The rapid expansion of day-case surgery in ophthalmology in the United Kingdom is a direct consequence of market forces, hitherto suppressed by the pre-Thatcherite superabundance of the old style NHS. No longer can ophthalmologists afford to ignore opportunities for undertaking most types of eye surgery under local anaesthesia and the increasing provision of day-case facilities in our hospitals is evidence of this.

The question of whether or not it is safe to perform surgery, particularly in elderly, frail, and/or sick patients, without the help of an anaesthetist has not as yet been properly addressed let alone answered. Many surgeons believe that an anaesthetist should always be close at hand and will not undertake an operating list even under local anaesthesia unless such help is available. Even if our anaesthetic colleagues are happy to administer or at least 'cover' local anaesthesia, however, anaesthetic staffing levels particularly for ophthalmic surgery are likely to decline sharply during the next decade as day-case surgery under local anaesthesia becomes the rule rather than the exception. Even vitreoretinal surgeons hitherto sheltering comfortably behind the complexities of their art may then come to feel the heat.

The paper by Cannon *et al* in this issue highlights the growing awareness among retinal surgeons, that even complicated vitreoretinal operations can be performed with safety and are tolerated well with local anaesthesia and that a proportion can be done as outpatient procedures.[1] Recent reports from the United States[2] and by our own group at Moorfields[3] have clearly demonstrated that advances in local anaesthetic techniques enable prolonged and complicated vitreoretinal surgery to be undertaken without undue stress to either the patient or the surgeon.

The complexities of preoperative work-up and postoperative management, however, frequently obviate the practice of day-case vitreoretinal surgery even when local anaesthesia is used,[4] while in regional centres for such specialist services where tertiary referrals form a high proportion of cases geographical, transportation, and other social considerations can render outpatient management impracticable. Nevertheless the facility to undertake surgery at short notice in patients who may not be fit for general anaesthesia is an obvious benefit of local anaesthesia especially when highly-skilled medical back-up is in limited supply, for instance at night or at week-ends, while the provision of hostel accommodation and improvements in local community nursing and other services may come to surmount such difficulties.

While the use of local anaesthesia for vitreoretinal surgery may not have such important financial implications as it does for less complicated forms of eye surgery the prospect of managing even a small proportion of our cases as outpatients must have an important bearing on the planning and provision of services in the future.

PETER LEAVER

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British Journal of Ophthalmology, 1992, 76, 66–67

Editorial

Cataracts in children with uveitis

Kanski, who has contributed significantly to the management of children with uveitis, now focuses on their 'complicated' cataracts, giving his authoritative views in this issue of *BJO*.

The frequency of uveitis in children is relatively low, approximately 8% of all cases of uveitis occurring in children under the age of 16.[1] Large series of patients with uveitis have been described by Kimura and Hogan,[2] by Perkins,[3] and by Jütte *et al.*[4]

In children, juvenile rheumatoid arthritis (JRA), also known as Still's disease, is the most common systemic association of chronic uveitis. Of 340 cases of systemic uveitis in childhood Kanski and Shun-Shin[5] found that 277 cases were associated with JRA. Juvenile ankylosing spondylitis (46 patients), juvenile psoriatic arthritis (nine patients), sarcoidosis (three patients), tuberculosis, Reiter's syndrome (one patient) and the Voght-Koyanagi-Harada syndrome (one patient) were the other underlying systemic disorders. Specific uveitis entities unassociated with a systemic disorder include pars planitis, Fuch's heterochromic cyclitis, and juvenile chronic iridocyclitis.[6]

In chronic anterior uveitis the anterior chamber reaction is often not gross but can persist for years. In most cases the onset is insidious and the disease is only discovered when the child is noted to have a difference in colour between the two eyes, a difference in the shape of the pupil, the onset of strabismus, or a white mark on the pupil or the cornea. Some are detected when being examined routinely after the diagnosis of arthritis is made.[7] Seventy per cent are bilaterally affected and 75% of the patients with JRA and uveitis are girls.[8]

Chronic uveitis in children often results in band keratopathy, cataracts, vitreous opacities, macular oedema and pucker, and glaucoma which, alone or in concert, progressively and insidiously impair vision.

Before starting treatment an underlying disorder should be excluded. It is preferable not to start systemic steroids before any immunological investigations are undertaken especially where tuberculosis and sarcoidosis may be suspected.

Steroids are still the mainstay of the management of uveitis. Though the chronic anterior uveitis can persist for many years in most cases it can be at least partly controlled by topical, periocular, or systemic steroids. Mydriatics may prevent but will rarely break down the posterior synechiae. It is usually best to give short acting mydriatic drops; they can, especially before synechiae have formed, be used at night causing fewer problems from the cycloplegia and mydriasis. The severe side effects of prolonged systemic steroids have often been the reason for using cytotoxic drugs in particularly severe cases of uveitis in adults: Dinning[9] however felt they should not be used in children. Martenet[10] on the other hand was impressed with the results of cyclophosphamide in the treatment of severe anterior uveitis in children.

One of the most frequent complications of a chronic anterior uveitis is the formation of cataracts. The term 'complicated' cataract has been used for many years[11] to describe the cataract which develops initially at the posterior pole of the lens as a polychromatic lustre surrounded by a cloudy haze. Later there is more extensive posterior and anterior subcapsular opacification, then the cortex is progressively involved until the cataract becomes mature.[12] The posterior synechiae may stimulate local cataract formation. The prolonged use of systemic or topical steroids can be partly responsible.

The management of complicated cataracts represents a surgical challenge which has been partly met by technological developments with improvement in the visual prognosis.

Intracapsular surgery and techniques which leave the posterior capsule intact are too prone to complications to be used routinely when lensectomy can be performed. Smiley[13] in 1974 reported no light perception in seven of 18 eyes within 2 months of cataract extraction by needling, intracapsular extraction, or aspiration techniques. Half of the JRA cataract patients treated by aspiration, extracapsular, or intracapsular extraction by Key and Kimura[14] had postoperative visual acuities of less than or equal to 20/200. Diamond and Kaplan conclude that it is advisable to minimise the preoperative inflammatory reaction by steroids or indomethacin.

The technique of choice today, as described by Kanski in this issue, is probably a lensectomy with lens fragmentation/aspiration and anterior vitrectomy, either by a limbal or pars plana approach. Diamond and Kaplan[15] performed pars plana lensectomy and vitrectomy on 13 patients (15 eyes) with complicated cataracts and preoperative visual acuities of 10/200 or less: postoperative acuities with a mean follow-up period of 10·5 months were 20/25 or better in eight eyes, 20/70 in two eyes and 20/100 to 20/400 in five eyes.

Nolthenius and Deutman[16] performed lens fragmentation/aspiration and pars plana vitrectomy on 21 patients (23 eyes) with chronic uveitis and cataracts. This resulted in all cases in an improved visual acuity with a mean follow-up time of 14 months. In four eyes the visual acuity only improved to 0·3–0·4. The primary cause of decreased vision postoperatively in both series was cystoid macular oedema. Flynn *et al*[17] retrospectively reviewed the results of the same technique in 10 eyes from seven JRA patients with secondary cataracts. Visual acuities improved from 20/100 or worse preoperatively to 20/60 or better postoperatively with a mean follow-up of 62 months.

From these and Kanski's series with a mean follow-up period of 5·4 years it is evident that this surgical approach results in an improved vision and can treat or prevent a number of complications.

Postoperative topical steroid treatment is necessary in most patients and a hard contact lens is often the best optical solution postoperatively. Because of the risk of synechiae and secondary membrane formation intraocular lens implantation is contraindicated.

In very small children amblyopia should not be overlooked. Failure of occlusion to improve vision can also be due to pupillary membranes, band keratopathy, cystoid macular oedema, or retinal detachment.

Kanski's paper will be read with interest by anyone involved in the management of these most challenging patients. The surgical techniques for management of complicated cataracts in uveitis have improved the visual prognosis for those patients whose vision is lost by cataract and it may also reduce the incidence of glaucoma, macular oedema, and perhaps of irreversible hypotony, and phthisis bulbi.

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ORIGINAL ARTICLES

Evaluation of outpatient experience with vitreoretinal surgery

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Abstract

The experience of 55 consecutive individuals undergoing outpatient vitreoretinal surgery was evaluated. Objective variables, including preoperative and intraoperative information, subjective postoperative pain, and discomfort were measured with a previously validated 100 mm visual analogue scale. Patients also ranked the overall experience. Average pain and discomfort scores in the recovery room were 21·8 and 22·6 and overnight were 26·7 and 30·4 (scale 0 to 100), respectively. Eighty eight per cent of subjects were satisfied with the experience. Elevated pain and discomfort scores were statistically correlated with scleral buckling, prolonged surgical or recovery room time, requirement for parenteral pain medications, and high intraocular pressure on the first postoperative visit. None of the patients needed further hospital treatment. This study suggests that vitreoretinal surgery in an appropriately selected population does not require routine inpatient care.

Health care has become increasingly focused on cost reduction, particularly on reduction of inpatient care, and conversion of traditionally inpatient procedures, such as cardiac catheterisation,[1] into outpatient treatment. However, hospital care remains common for patients undergoing vitreoretinal surgery for the repair of retinal detachment and other diseases of the retina. Isernhagen and associates[2] recently reported on a series of 200 consecutive inpatients undergoing vitreoretinal surgery. They concluded that many factors, including excessive pain, nausea, and vomiting, occurred frequently enough to necessitate routine overnight stay in hospital.

Outpatient procedures may reduce costs significantly and may offer psychological benefit to the patient. Recent experience at our institution has suggested that, with the exception of small children and diabetics, many patients tolerate outpatient vitreoretinal surgery quite well if proper precautions are taken to prevent complications which require hospital care. It was our impression that most of the cited reasons for inpatient care, such as severe nausea, are often the result of systemic anaesthetics rather than the surgery itself. We prefer local anaesthesia in conjunction with mild, short acting intravenous sedation for vitreoretinal surgery. General anaesthesia, though conducive to patient immobility during long procedures, may require a longer, more uncomfortable postoperative recovery period.[3] To maintain adequate anaesthesia during the longer operations we found that irrigation of the peribulbar tissue with a 4% lignocaine with 0·75% bupivacaine solution through a blunt cannula was efficacious. Increased intraocular pressure can usually be controlled with perioperative carbonic anhydrase inhibitors.

Scleral buckling is another significant source of pain. Unlike the retina, which is devoid of pain fibres, the sclera is innervated by free nerve endings of the trigeminal nerve.[4] In many of our patients undergoing vitreoretinal surgery we no longer perform extensive scleral buckling. Patients referred for proliferative vitreoretinopathy at our institution usually have already received encircling scleral elements which we rarely revise. In eyes requiring vitreous surgery and encircling buckles, a relatively small 7·5–9·0 mm encircling element is inserted to support the vitreous base and relieve any residual traction internally. We usually treat uncomplicated retinal detachments by segmental buckling performed under local anaesthesia.

We undertook a prospective study to analyse patient discomfort and experience with outpatient vitreoretinal surgery using objective and subjective data obtained from consecutive outpatients. We sought to determine (1) what percentage of patients tolerate outpatient vitreoretinal surgery, (2) the factors that are associated with a favourable or unfavourable outpatient experience, and (3) overall patient satisfaction with the outpatient setting.

Materials and methods

Subjects included 55 consecutive patients undergoing vitreoretinal surgery by a single surgeon (WRF). Patients had the choice of general or local anaesthesia with intravenous sedation using primarily fentanyl citrate and midazolam hydrochloride. Patients were encouraged to have local anaesthesia to reduce postoperative discomfort and hasten recovery. Before discharge, the intraocular pressure in those patients who received intraocular gas was measured and found to be below 35 mm Hg. All patients had received intravenous or oral acetazolamide immediately postoperatively.

Two groups of patients were studied. One

Table 1

Preference statements; please choose one.
(1) I was comfortable going home on the same day as my surgery knowing I would see the doctor today There was no reason for me to stay overnight in the hospital
(2) I was concerned about leaving the hospital on the same day as my surgery. I would have felt more comfortable if I had stayed overnight but it worked out okay
(3) I should have stayed overnight at the hospital after my surgery I was in considerable pain and discomfort at home

consecutive series of patients were retrospectively contacted by letter. Another consecutive series of patients were studied prospectively, interviewed in the clinic on the first postoperative day with medical data collected at that time. Patients under 15 years old were excluded from the study.

The preoperative objective information included age, sex, number of previous surgeries on the operated eye, and medical history. The intraoperative information included type of anaesthesia (general or local), type of procedure performed (trans par plana vitrectomy, scleral buckling, intraocular long-acting gas injection and/or intraocular silicone oil injection), operated eye, and surgical time in minutes. In all cases, gas or silicone oil injections were performed in conjunction with pars plana vitrectomy surgery. No patients in this study underwent pneumatic retinopexy as that procedure is performed in the clinic at our institution. The postoperative factors analysed were time from completion of operation to hospital discharge in minutes, type of analgesia received in the recovery room, ocular status on the first postoperative day as assessed by the surgeon, including intraocular pressure in the operated eye, status of the cornea, degree of inflammation, attachment of retina, and presence of vitreous haemorrhage.

Data obtained after surgery included type and amount of analgesics taken, whether the ophthalmologist was called after discharge from hospital, a three-point preference scale regarding outpatient treatment (Table 1) and a series of standardised visual analogue scales to measure pain and discomfort (Fig 1) for the periods in the recovery room, overnight and, in the case of prospective patients, at the time of interview.

Predictors, defined as preoperative, intraoperative, or postoperative, were compared individually with each of the subjective outcome measures using χ^2, *t* test, or simple regression, as appropriate. All data were analysed using StatView 512 (BrainPower, Inc, Calabasas, CA, USA) on a Macintosh SE computer.

Table 2 Medical conditions and procedures performed

	Total number	*Per cent*
Medical conditions		
None	31	56·0
Diabetes	5	9·1
Hypertension	14	25·0
Heart disease	6	10·9
Acquired immunodeficiency syndrome	4	7·3
Procedures		
Trans par plana vitrectomy	48	87·3
Scleral buckle	23	41·8
Intraocular gas	17	31·0
Silicone oil	17	31·0

Table 3 Ocular status on postoperative day one

	Number of patients	*Per cent*
Intraocular pressure >40 mm Hg	2	3·6
Oedematous cornea	19	36·0
Retina attached	52	98·0
Vitreous haemorrhage	7	13·0
Inflammation		
None	7	13·2
Mild	21	39·6
Moderate	18	34·0
Severe	7	13·2

Table 4 Pain and discomfort score summary

	Mean	*SD*	*Range*	*No >75*	*%>75**
Recovery room					
Pain	21·8	29·6	0–100	6	11·0
Discomfort	22·6	30·3	0–100	7	12·7
Overnight					
Pain	26·7	30·7	0–98	7	12·7
Discomfort	30·4	29·7	0–99	7	12·7

*Indicates percentage of patients with a pain or discomfort score over 75 which indicates moderately intense pain or discomfort

Results

A total of 55 patients, 33 males and 22 females, ages 22 to 90, were studied – 37 patients, 22 males and 15 females, were studied prospectively. Their average age was 54 years, range 22 to 86. Eleven males and seven females responded to the mailed questionnaire. Five males and two females did not respond, were unreachable, refused the study, or did not fill out the questionnaire correctly. The average age of these patients was 62·5 years old (ranging from 24 to 90). All but two participating patients had local retrobulbar anaesthesia and two thirds had a history of previous eye surgery. Underlying medical problems and procedures and their frequencies are listed in Table 2. Surgical time ranged from 30 to 245 minutes, and averaged 120 minutes.

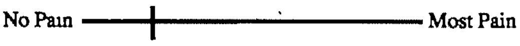

Figure 1 Example of the highly validated visual analogue scale for measuring pain. The patient is asked to place a vertical mark across the horizontal line indicating intensity of pain with 'most pain' indicating the most severe pain the patient has experienced. The scale is linear with zero assigned to 'no pain' and 100 assigned to 'most pain'. In this case, the score is 20.

Time to hospital discharge averaged 131 minutes, ranging from 45 to 375 minutes. Nine per cent of patients required parenteral analgesia in the recovery room. Ocular status on the first postoperative day is summarised in Table 3.

Only one patient had pain that required parenteral analgesia after hospital discharge. Ten per cent of the patients called the physician between discharge and the first postoperative day visit. Seventy eight per cent of patients chose statement number 1 that indicated they preferred outpatient treatment to the option of an overnight stay in hospital, with an additional 10 per cent choosing statement number 2. Pain and discomfort scores from the visual analogue scales are summarised in Table 4. A score of more than 75 was taken to indicate severe pain.[5,6] No patients required readmission to hospital following their initial discharge.

Several objective measures significantly correlated with elevated pain and discomfort scores: scleral buckling (p=0·02), prolonged surgical time (p=0·03), prolonged recovery room time (p=0·04), requirement of parenteral analgesia in the recovery room (p=0·005), post-discharge telephone call to the physician (p=0·02), and elevated intraocular pressure as measured on the first postoperative day (p=0·004). The retrospective data were compared with the prospective data and no difference in conclusions existed. Intraocular pressure elevation did not cause visual loss in any patient.

Comment

The results of this study indicate that vitreoretinal surgery can be performed as an ambulatory procedure in the majority of our patient population. Our study population of outpatients was preselected to include individuals deemed by the surgeon to be good outpatient risks. We excluded poorly controlled insulin-dependent diabetics who are known to have difficult postoperative courses regardless of the type of operation, particularly those undergoing general anaesthesia.[7] They are routinely treated as inpatients at our institution not because of postoperative pain and discomfort but rather to optimise postoperative medical management of their underlying disease. We studied both a consecutive retrospective and prospective series of patients; analysis of both groups and the total population gave the same results.

This study suggests that routine inpatient care of all vitreoretinal surgery patients is unnecessary using newer anaesthetic techniques.[8] A significant proportion can undergo surgery in the outpatient setting, and these patients appreciate such a treatment.

Our results contrast with those of Isernhagen[2] who studied a strictly inpatient population and concluded that an overnight stay in hospital was required in nearly all vitreoretinal surgical patients because of postoperative pain and discomfort. Our study population differs only in the proportion of diabetics (9·1% in our study versus 35% in theirs), because complicated, insulin-dependent diabetics are routinely managed postoperatively as inpatients at our institution.

We attempted a more rigorous design to measure the subjective pain and discomfort of patients through the use of the visual analogue scale, a linear scale used by patients to indicate visually their level of pain or discomfort, and a choice of preference statements. However, the visual analogue scale, by translating a continuous-scale perception into a continuous scale on paper, is considered the most valid and reliable method for this purpose.[5] This tool has been successfully used and validated in studies regarding pain associated with dental work,[6 9] rheumatoid arthritis,[10] and elective gallbladder surgery.[11] We were careful to ensure that all patients studied had adequate vision in at least one eye and adequate understanding of the scale to ensure reliability.

Certain variables are correlated with higher pain and discomfort during the immediate postoperative 24 hours. Each deserves comment: (1) scleral buckling; this would be expected to induce more pain and discomfort due to intraoperative traction of the extraocular muscles, and the presence of a foreign body on the sclera. (2) Longer surgical time; this is in agreement with another study[12] that cited factors associated with unplanned admissions following outpatient ophthalmic procedures. (3) Longer time to discharge; reasons why the patient stayed longer in the recovery room were not easily accounted for. However our postoperative questioning of patients suggests that they may be related to perioperative pain and discomfort, problems in ambulation, non-medical problems (eg transportation), and other factors. (4) Those who required parenteral analgesia in the recovery room were experiencing pain that could not be relieved by oral medications and their scores, not surprisingly, reflected this observation. (5) Reasons for a late night call to the doctor did not result in readmission to hospital; the calls involved reassurance, postoperative advice, and instructions on the use of medications. (6) High intraocular pressure (>40 mm Hg) is known to be painful and patients with increased intraocular pressure on the first postoperative day would be expected to have higher intraocular pressure immediately postoperatively[13] which contributed to their pain. It is of note that elevated intraocular pressure did not cause vision loss in any of our patients.

Though the above significant correlations were found they do not necessarily predict a need for inpatient care, but rather provided some indicators of an increased need for analgesia or personal follow up. Our postoperative questioning suggested that the outpatient setting was associated with greater vigilance in maintainence of special positioning. This was secondary to the presence of supportive family members compared with the alternative of busy hospital nurses who may be less informed about the importance of positioning. It is possible that this would result in improved surgical outcome.

It is interesting to note that there was no significant difference in pain or discomfort scores between genders or ages, nor between those who did and did not receive silicone oil intraocularly.

Our study agrees with Wilson and Barr[14] who retrospectively reviewed a series of vitreoretinal surgery cases performed under general anaesthesia and in hospital with local anaesthesia and outpatient treatment. Our results apply to patients who meet our criteria for being good outpatient risks, including the absence of serious or uncontrolled concomitant medical conditions and the ability to tolerate and cooperate with local anaesthesia during a potentially long procedure. We prefer smaller encircling elements and emphasise internal relief of traction over extensive scleral buckling. In many cases, our patient population entailed re-operations or other surgery where scleral buckling was not employed.

Patients appropriate for outpatient management must be able to follow postoperative directions regarding special positioning, medications, follow up, and other relevant instructions. They must have a place to stay, a responsible party to provide transport, and a postoperative carer in close proximity for at least the first 24 postoperative hours. In our experience, insulin-dependent diabetics are generally not good candidates for ambulatory vitreoretinal surgery. Paediatric patients without serious underlying medical problems can tolerate outpatient surgery but the need for general anaesthesia generally necessitates a longer recovery room stay.

Dr Gross is presently at the University of South Carolina School of Medicine, Columbia, SC, USA

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Lensectomy for complicated cataract in juvenile chronic iridocyclitis

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Abstract

Experience with the removal of complicated cataract by lensectomy in patients with juvenile chronic iridocyclitis (JCI) has so far been limited. The results of lensectomy were reviewed retrospectively in 131 patients with JCI (187 eyes). The mean follow up period was 5 years 4 months. The main operative complication was accidental loss of lens material into the vitreous cavity. The postoperative complications were glaucoma (23 eyes, 15%), phthisis (14 eyes, 8%), secondary pupillary membranes (11 eyes, 6%), and retinal detachment (six eyes, 3%). The incidence of postoperative phthisis was related to the level of intraocular pressure (IOP) at the time of surgery. Twenty four per cent of hypotonous eyes and 4% of eyes with normal or elevated IOP became phthisical. Visual acuity was improved in 77%, was worse in 13%, and unchanged in 10% of eyes. The main causes of a postoperative visual acuity of 6/60 or less were glaucoma, amblyopia, and phthisis. Lensectomy did not appear to alter the course of uveitis.

Cataract is a common complication of chronic iridocyclitis particularly in patients with associated juvenile chronic arthritis (JCA) where the reported incidence is about 30%.[1,2] In the past the prognosis of lens extraction was poor mainly due to technical difficulties which resulted in incomplete removal of lens cortex and capsule. The need for re-operation for secondary pupillary membranes frequently resulted in exacerbation of the uveitis and the subsequent development of chronic hypotony and blindness.[3-6] Most of these problems can be overcome by using an automated cutting instrument. Because juvenile chronic iridocyclitis (JCI) is relatively rare the literature contains a few sporadic cases treated by this technique. The follow up in most series is also relatively short. This communication presents the long term results of a large series of patients.

Patients and methods

During early 1991 the records of 136 consecutive patients treated for cataracts secondary to JCI by lensectomy were reviewed. All were managed during a 15-year period (1976–90;). Follow up data of five patients (six eyes) were unavailable. The remaining 131 patients (187 eyes) were reviewed retrospectively and the following data recorded: sex, presence of arthritis, age at the time of surgery, length of follow up, operative and postoperative complications, and visual results.

Juvenile chronic iridocyclitis was defined as a specific type of intraocular inflammation which developed before age 16 years. The uveitis was non-granulomatous, frequently bilateral, and usually had an insidious and asymptomatic onset. Band keratopathy and posterior synechiae were frequently seen in longstanding cases. Of the 131 patients (82 female and 49 male) with JCI, 100 had associated JCA, three had juvenile spondylitis, and 28 had no associated systemic disease (Table 1). The diagnosis of arthritis was made by a paediatric rheumatologist following appropriate investigations. The average age at the time of cataract surgery was 12 years 7 months (range: 3–40 years). The intraocular pressure at the time of surgery was more than 21 mm Hg in 37 (20%) and less than 10 mm Hg in 29 (16%) of the 187 eyes. Preoperative visual acuities ranged from 6/12 to hand movements.

PREOPERATIVE PREPARATION

Eyes with active uveitis were treated with dexamethasone drops at 2-hourly intervals for 2 days prior to surgery. Systemic corticosteroids were not used. An attempt was made to dilate the pupil with atropine 1% the day before surgery and phenylephrine 10% every half hour for 2 hours immediately prior to surgery. All operations were performed under general anaesthesia.

SURGICAL TECHNIQUES

Lensectomy was performed through one incision with the infusion sleeve placed over the probe either at the limbus (97 eyes) or pars plana (90 eyes). The pars plana technique was as follows. A stab incision was made with a knife into the lens 3·5 mm posterior to the limbus. The probe was introduced into the lens and small pupils were enlarged. The lens was excised from within the capsular bag. Soft lens matter was removed by suction alone while harder pieces were excised by activating the cutting mode. The cutting port was then positioned posteriorly to excise the posterior capsule and the anterior third of the vitreous gel. Finally the anterior capsule was excised. The sclerotomy was sutured and an inferior sub-Tenon's injection was given of

Table 1 Patient characteristics

Aetiology of uveitis	*Number of patients* *Female*	*Male*	*Number of eyes*
Juvenile chronic arthritis	62	38	139
Juvenile spondylitis	0	3	5
Idiopathic	20	8	43
Subtotals	82	49	187

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gentamicin (20 mg) and either methylprednisolone acetate (20 mg) or triamcinolone acetonide (20 mg). The technique of lensectomy via the limbus was similar except that the incision was made in peripheral clear cornea.

In seven eyes the lens nucleus was too hard to be removed with the cutter. In these cases a large corneal incision was made and the nucleus was expressed manually. Residual soft lens matter together with the capsule and anterior vitreous were excised with the cutter. In eight eyes the anterior capsule was covered by a dense rubbery plaque attached to the surrounding iris which could not be excised with the cutter. In these cases the plaque was first cut with scissors into several pieces and then each piece was removed separately with forceps or the cutter. In one eye a dense retrolenticular cyclitic membrane was excised in a similar manner. In some eyes calcified lenticular flakes that could not be aspirated into the cutter were removed with forceps. In two eyes intraocular diathermy was used to control bleeding from the iris. Combined procedures were performed in 17 eyes (trabeculodialysis 11, chelation five, trabeculodialysis combined with chelation one).

POSTOPERATIVE MANAGEMENT

During the immediate postoperative period all eyes showed a severe surgically-induced exacerbation of uveitis which was treated with the frequent use of dexamethasone drops. The rate of instillation was then adjusted according to the severity of inflammation. With the passage of time the aqueous flare gradually became less dense but in the majority of cases some degree of flare persisted indefinitely. At follow up only four eyes had a longlasting and complete resolution of uveitis.

Results

A total of 187 eyes in 131 patients were available for analysis. The mean follow up period was 5 years 4 months (range: 1 month–15 years).

OPERATIVE COMPLICATIONS

In 14 eyes lens fragments were accidentally dislodged into the vitreous. Small fragments in nine eyes were left. In five eyes the fragments were large; in three of these they were left and in two they were retrieved with the cutting probe. The three large lens fragments which were left subsequently appeared in the anterior chamber during the postoperative period. In one case the lens material was removed with the cutter without complications. One of the two remaining eyes developed corneal decompensation due to endothelial damage which later necessitated penetrating keratoplasty and the other eye developed intractable glaucoma and was enucleated.

Table 2 Postoperative complications

Complication	*Number of eyes (%)*
Glaucoma	23/150 (15)
Phthisis	14/187 (8)
Secondary membranes	11/187 (6)
Retinal detachment	6/187 (3)

POSTOPERATIVE COMPLICATIONS

Details of postoperative complications are shown in Table 2.

1. Secondary glaucoma

Fifteen per cent (23) of the 150 eyes that did not have glaucoma preoperatively subsequently developed persistently raised intraocular pressure. The mean interval between cataract surgery and the diagnosis of glaucoma was 3 years (range: 3 months–10 years). When last examined four of these eyes had no light perception and two had been enucleated.

2. Phthisis bulbi

Twenty four per cent (seven) of the 29 eyes with an intraocular pressure of less than 10 mm Hg at the time of surgery became phthisical, usually within a few weeks of surgery. Of the remaining 22 eyes 12 regained a normal intraocular pressure, one developed glaucoma, and nine remained soft. Four per cent (seven) of the 158 eyes that were not hypotonous at the time of surgery subsequently developed phthisis. The overall incidence of postoperative phthisis was 8% (14) of the 187 eyes.

3. Secondary pupillary membranes

Six per cent (11) of the 187 eyes developed secondary pupillary membranes. In seven eyes the membranes developed within the first few postoperative days either as a result of very severe surgically induced exacerbation of uveitis (four) or the presence of blood in the pupil (three). In the remaining four eyes the membranes consisted of residual opacified posterior capsule that had been inadequately excised during lensectomy. In 10 eyes the membranes were subsequently excised surgically, and in one eye the membrane was treated with a Nd:YAG laser.

4. Retinal detachment

Three per cent (six) of the 187 eyes developed retinal detachment. The mean interval between cataract surgery and the diagnosis of retinal detachment was 2 years 5 months (range: 2 months–7 years 6 months). In two eyes retinal surgery was not performed because of poor visual prognosis. Successful retinal reattachment was achieved in three of the remaining four eyes.

VISUAL RESULTS

Visual acuity was improved in 77% (144), it was worse in 13% (24), and unchanged in 10% (19) of the 187 eyes. Table 3 shows the pre- and postoperative visual acuities in relation to the follow up period. Table 4 shows the causes of a postoperative visual acuity of 6/60 or less. The mean age at the time of surgery of patients with amblyopic eyes was 5 years.

Table 3 Visual results in relation to follow up

Visual acuity	Follow up (months) 1–35	36–71	72–107	108–143	144–180	Number of eyes (%)
HM–no PL	9	6	5	10	7	37 (20)
CF–6/60	17	7	5	6	2	37 (20)
6/36–6/24	6	1	2	1	0	10 (5)
6/18–6/12	10	4	2	3	1	20 (10)
6/9–6/6	37	15	9	15	7	83 (45)
Subtotals	79	33	23	35	17	187 (100)

HM=hand movements.
PL=percetion of light
CF=counting fingers.

Discussion

In analysing the results of this study it is not possible to apply the same criteria as for senile cataracts because of the completely different problems encountered in eyes with chronic iridocyclitis. For example 36% of eyes had either secondary glaucoma or hypotony at the time of surgery and the majority had persistent inflammation following cataract extraction. In addition the poor visual results in some cases were caused by amblyopia.

Secondary glaucoma developed postoperatively in 15% of the eyes with frequently devastating effects. It can be speculated that some eyes would have developed glaucoma had cataract extraction not been performed. However it is probable that in the majority of cases the development of glaucoma was either accelerated by or directly caused by cataract surgery. It seems likely that the postoperative surgically induced exacerbation of intraocular inflammation enhanced the development of secondary angle closure by the formation of peripheral anterior synechiae.

The incidence of phthisis bulbi was in part related to the level of intraocular pressure at the time of cataract surgery (that is 4% in eyes that were not hypotonous and 24% in soft eyes). In the past hypotony was considered to be a contraindication to cataract surgery. However this study shows that the presence of hypotony at the time of lensectomy did not necessarily mean that postoperative phthisis was inevitable because 45% of soft eyes either regained a normal intraocular pressure or became glaucomatous during the postoperative period. It therefore appears that if lensectomy is performed in a 'prephthisical' eye the progressive downhill course to complete phthisis may be halted or even reversed. The exact mechanism by which lensectomy combined with anterior vitrectomy may result in a return to normal of secretion of aqueous by the ciliary epithelium is speculative. It can be postulated that the excision of an invisible 'cyclitic membrane' which is causing ciliary shutdown secondary to detachment of the ciliary body is a possible mechanism in some cases. However the author was able to identify a true cyclitic membrane at the time of surgery in only one eye.

Table 4 Causes of poor postoperative visual acuity

Cause	Visual acuity (number of eyes) No PL–HM	CF–6/60	Subtotals
Glaucoma	17	4	21
Amblyopia	1	14	15
Phthisis	14	0	14
Hypotony	0	8	8
Maculopathy	1	7	8
Retinal detachment	4	0	4
Keratopathy	0	3	3
Unknown	0	1	1
Subtotals	37	37	74

PL=perception of light.
HM=hand movement
CF=counting fingers

One of the main theoretical advantages of lensectomy over other techniques is its ability to eliminate the 'scaffold' (that is posterior capsule and anterior vitreous gel) along which secondary membranes can grow postoperatively. Despite this 6% of the eyes still developed secondary pupillary membranes. In four eyes secondary membrane formation could have been prevented by taking greater care to perform a more complete excision of the posterior capsule at the time of lensectomy. In the remaining seven cases secondary membrane formation was probably unavoidable as it occurred during the immediate postoperative period as a result of either a severe exacerbation of intraocular inflammation or the presence of organised blood within the pupil.

Analysis of the visual results should be interpreted with caution because, even following a perfectly performed lensectomy, the visual acuity may be poor due to other complications of uveitis. It is however important to point out that several aphakic eyes remained unscathed and maintained excellent visual acuity for several years. For example 50% of aphakic eyes maintained a visual acuity of 6/18 or better after a follow up period of 9 years or more (Table 3).

Amblyopia was the second most common cause of a final visual acuity of 6/60 or less. A poor visual result in a young child should not be attributed to mild band keratopathy or questionable macular oedema with the possibility of amblyopia being overlooked. It is also important not to delay cataract surgery unnecessarily because the longer the delay the worse will be the results of anti-amblyopia therapy.

It is difficult to draw meaningful comparisons between this series and other reports because of variations in instrumentation, technique of lens removal, extent of excision of the vitreous gel, and period of follow up. Flynn *et al*[7] operated on seven patients (10 eyes) with JCI associated with JCA using a three incision pars plana approach with excision of the posterior vitreous in all cases. After a mean follow up of 2 years 4 months all 10 eyes had a visual acuity of 20/70 or better. The two major obstacles to good vision in eyes that had successful surgery were persistent macular oedema and poor control of pre-existing glaucoma.

Diamond and Kaplan[8] performed lensectomy on 25 eyes of 20 patients for complicated cataracts due to various forms of uveitis. They used a pars plana approach and performed a subtotal vitrectomy. The two patients with JCI also had JCA. The postoperative visual acuities were 20/20 and 20/70, but no details were given of the period of follow up.

Dangel *et al*[9] reported the results of lensectomy in eight eyes of five patients with various forms of uveitis. They used a two incision limbal approach with a separate incision for the infusion cannula and performed a partial anterior vitrectomy. Of the two patients with JCI, one had juvenile spondylitis (two eyes) and the other JCA (one eye). The postoperative visual acuities were 20/40 (two eyes) and 20/80. No complications were encountered after a mean follow up of 11 months.

Tutein Nolthenius and Deutman[10] performed lens removal through a pars plana incision of 19 cataracts in patients with various forms of uveitis. Although details of the age of the patients at the time of surgery and the types of uveitis were poorly documented it appears that in the two patients (two eyes) with JCI and JCA the postoperative visual acuities were 6/18 and 6/12. No complications were reported after a mean follow up of 1 year 8 months. Visual results of lensectomy in JCI in other isolated reports were 20/25 (two eyes) and 20/200,[11] 20/50 and 20/80,[12] 20/30 and counting fingers,[13] and 20/70.[14]

Whether lensectomy-vitrectomy alters the pattern of uveitis is difficult to answer because only careful observation over a very long period of time is likely to reveal a significant change in pattern. Diamond and Kaplan[8] noted an apparent decrease in the severity of recurrent episodes of uveitis after a mean follow up of 1 year 3 months. They speculated that lensectomy-vitrectomy may be beneficial by providing an unobstructed pathway that facilitates the removal of cellular debris from the vitreous cavity. It has also been postulated that the maintenance and/or relapse of intraocular inflammation may be associated with the presence of antigen-specific 'memory cells' in the vitreous cavity.[10] The mechanical removal of these cells together with immune complexes may in some way modulate the course of the uveitis. In this study only 2% of the eyes had a complete and long lasting cessation of uveitis activity following lensectomy. The mean follow up in these four eyes was 9 years 6 months. It is important to point out that whereas Diamond and Kaplan[8] performed a subtotal vitrectomy in all eyes the author performed only an anterior vitrectomy. It is possible that a more extensive excision of vitreous gel might have been more beneficial.

In conclusion, it appears that lensectomy is a good technique for the removal of soft complicated cataracts in patients with JCI. The risk of postoperative phthisis is small provided the intraocular pressure is not low at the time of surgery. Lensectomy does not appear to alter the course of chronic iridocyclitis.

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An experimental model of oculorespiratory reflex

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Abstract

An experimental study of the oculorespiratory reflex (ORR) was conducted on 20 albino rabbits using a square wave (SW) type of stimulus. The ORR could be elicited in 100% of animals. The medial rectus was observed to be most reflexogenic for ORR. The frequency and pattern of ORR was not affected by bilateral vagotomy, intravenous atropine or glycopyrrolate, but could be completely abolished by retrobular block.

The oculorespiratory reflex (ORR), which manifests as slowing of respiratory rate and/or respiratory rhythm changes due to pressure or manipulation of the eye, was first described by Aschner[1] in rabbits. It was later elicited by evoking pressure on human eyes.[2] Since then little attention has been paid to it till a recent article in which Blanc *et al*[3] reported that ORR is a frequent and potentially dangerous occurrence during extraocular muscle traction. Therefore the present experimental work was planned to study the different aspects of occurrence and prevention of the ORR.

Table 1 Patterns of oculorespiratory reflex

Pattern of oculorespiratory reflex	*No. of rabbits*	*%*
1 Slowing of respiration only	6	30
2 Apnoea followed by irregular respiration	7	35
3 Irregular respiration followed by rapid shallow breathing	7	35
Total	20	100

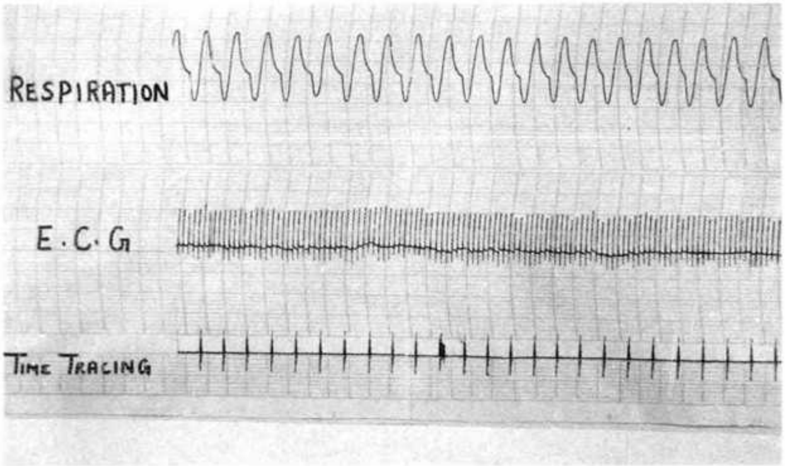

Figure 1 Basal record of respiration and electrocardiograph.

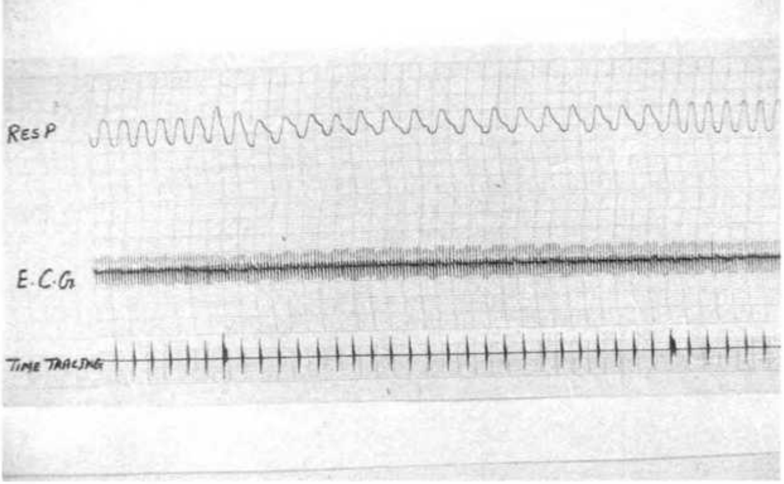

Figure 2 Positive ORR. Pattern I: slowing of respiration.

Material and methods

Experiments were carried out on 20 albino rabbits of either sex weighing between 1 and 2 kg. Overnight fasting rabbits were anaesthetised with intravenous pentobarbitone (40 mg/kg body weight). Tracheostomy was performed for endotracheal intubation. The vagi were separated in the cervical region. The femoral vein of one side was cannulated for intermittent injection of anaesthetic and infusion of drugs. Respiration was recorded from a tracheal cannula by a transducer on Polyrite (Inco). The electrocardiogram was recorded by needle electrodes.

All four rectus muscles – medial (MR), lateral (LR), superior (SR), and inferior (IR) were exposed by a gently performed perilimbal peritomy and a silk suture loop was passed under each muscle. A silk suture with wire hooks on both ends was passed over a pulley fixed on a stand. One hook was engaged in the silk suture loop under the muscle tendon and on the other weights were attached.

In each rabbit, after taking the basal recording of respiration and ECG, traction with a 150 g weight was applied by a square wave (SW) type of stimulus (acute traction sustained for a minimal period of 20 seconds followed by acute release) to medial rectus and changes in heart and respiratory rate as well as rhythm were recorded. The procedure was repeated for lateral, superior, and inferior recti after a pause of 3 minutes. For further study the 20 rabbits were divided into four groups of five rabbits each. In group I, after taking the basal recordings, bilateral vagotomy was performed in the cervical region and its effects on ORR were elicited by a SW stimulus to the medial rectus only. Similarly effects of intravenous atropine (15 µg/kg body weight), intravenous glycopyrrolate (7·5 µg/kg body weight), and retrobulbar block (after 10 minutes of injection of 2 ml of 2% xylocaine) were elicited in rabbits in groups II, III, and IV, respectively.

A fall in respiratory rate of 10% or more and/or respiratory rhythm changes and/or development of shallow respiratory movements during muscle

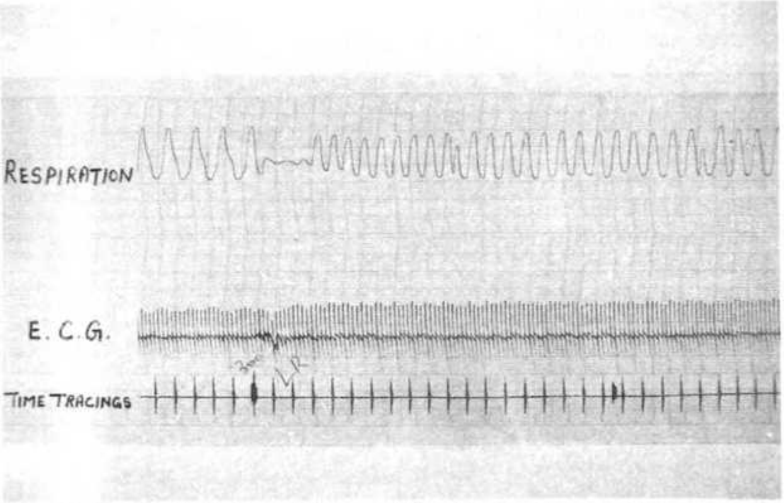

Figure 3 Positive ORR. Pattern II: apnoea followed by irregular respiration.

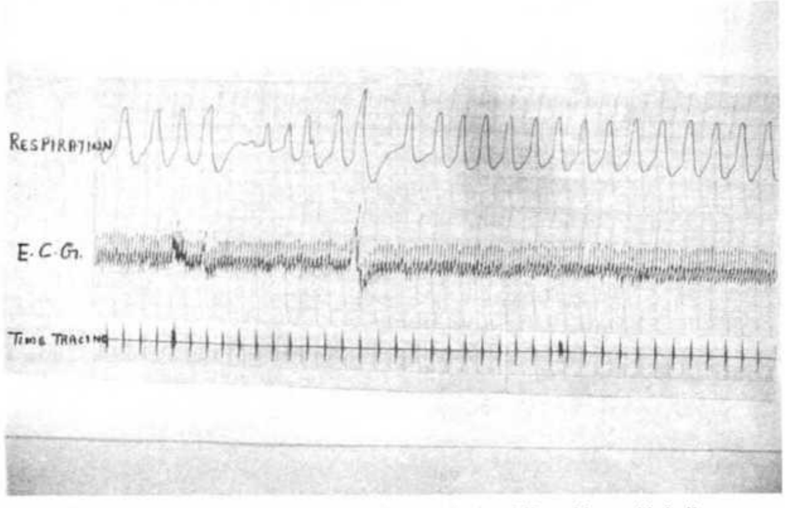

Figure 4 Positive ORR. Pattern III: irregular respiration followed by rapid shallow breathing.

traction was the criterion considered for positive ORR.[3]

Results

All 20 animals (100%) exhibited positive ORR on extraocular muscle traction. The frequency of ORR on stretching lateral, superior, and inferior rectus muscles was identical (90% each), while the medial rectus was observed to be more sensitive (100%). As shown in Table 1 three different patterns of ORR were observed in this experimental study. Slowing of respiratory rate was observed in six (30%), apnoea followed by irregular respiration in seven (35%) and irregular respiration followed by rapid shallow breathing in seven (35%) animals. The basal recordings and the three patterns of ORR observed are shown in Figs 1 to 4. Occurrence of ORR was observed in 100% of animals after vagotomy and intravenous atropine as well as glycopyrrolate; while none of the animals demonstrated positive ORR after retrobulbar block (Table 2).

Discussion

The SW stimulus was chosen in the present experimental model as it is considered highly reflexogenic.[4] The oculorespiratory reflex could be elicited in all the animals studied. Our results are similar to those of Blanc *et al*[3] who noted ORR in 100% of the cases studied using an SW traction of 200–250 g lasting for 10–15 seconds. Joffe and Gay[5] also observed ORR in all the cases by uniocular or binocular manual pressure on the eyeball.

In the present study the medial rectus was observed to be most sensitive, as 100% of the muscles on stretching demonstrated positive ORR in comparison to 90% each with LR, SR, and IR. In the available literature we could find no study relating the incidence of ORR with the muscle stretched. However higher sensitivity of the MR as regards occurrence of oculocardiac reflex (OCR) is well documented in the literature.[6 7]

We have observed three different patterns of ORR (Table 2, Figs 2 to 4). Blanc *et al*[3] reported slowing of respiration, and/or shallow respiratory movements in each patient and apnoea of 20 seconds duration in only one patient. Joffe and Gay[5] noticed expiratory pause by uniocular or binocular manual pressure and apnoea, and respiratory arrhythmia occasionally leading to irregular respiratory arrest by intraorbital and intracranial stimulation.

In the present study no effect of vagotomy, atropine, or glycopyrrolate was seen on the ORR, which could be completely abolished by retrobulbar block (Table 2). Delva[8] also could not prevent ORR after bilateral vagotomy and section of the spinal cord at the level of the seventh cervical vertebra (phrenic nerve intact) on dogs. Patizetakis[2] noted a similar response and reported that atropine does not change the incidence of ORR. However Delva[8] like Joffe and Gay[5] demonstrated that atropine enhances the ORR. In the available literature we could trace no study on the effects of glycopyrrolate and retrobulbar block on ORR. Our observations clearly reflect that the efferent pathway of ORR must be different from that of OCR, as the latter could be abolished by vagotomy,[8] intravenous atropine,[4] and glycopyrrolate.[9] Therefore it seems that OCR and ORR are not interrelated but are independent of each other. However Blanc *et al*[3] have reported a high incidence of OCR in patients with hypoxia. Hence it is tempting to speculate that ORR by producing hypoxia might be increasing the incidence of OCR.

The results of the present study fully corroborate the views of Blanc *et al*[3] that ORR is a frequent and potentially dangerous occurrence during extraocular muscle traction. However this reflex is not widely recognised by ophthalmologists or anaesthesiologists. This phenomenon may not be recognised in the centres where

Table 2 Frequency of oculorespiratory reflex before and after treatment in different groups

Group	Total no. of rabbits	Rabbits with positive ORR (%)	
		Before treatment	After treatment
Group I (vagotomy)	5	5 (100)	5 (100)
Group II (atropine)	5	5 (100)	5 (100)
Group III (glycopyrrolate)	5	5 (100)	5 (100)
Group IV (retrobulbar block)	5	5 (100)	0

squint patients are anaesthetised with controlled ventilation. Many anaesthetists may still be using spontaneous respiration. ORR is often ignored by the anaesthetist who responds by introducing assisted or controlled ventilation so that the significance of the reflex is overlooked.

These significant results in the rabbit may suggest a similar phenomenon in the human patient and would strengthen the case for further research. There is little evidence of patients having suffered a fall in oxygen saturation or a rise in carbon dioxide for a sufficient period to have clinical significance. There may be a case for encouraging controlled ventilation during squint surgery.[3] The results of the present study in preventing ORR with retrobulbar injection are in close agreement with those of Mandelblatt *et al*,[7] who have recommended its routine use to block the OCR in all cases of local or general ophthalmic surgery, and also agrees with the results of Kirsch *et al.*[10]

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Biological activities of vitreous gel, retrohyaloid fluid and subretinal fluid from diabetic and non-diabetic eyes

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Abstract

This study compared the effects of vitreous gel, retrohyaloid fluid and subretinal fluid from diabetic and non-diabetic eyes on the proliferation and migration of retinal microvascular cells in vitro. Intraocular fluids were obtained from eyes undergoing repair of retinal detachment, due either to proliferative diabetic retinopathy or rhegmatogenous retinal detachment associated with a degree of proliferative vitreoretinopathy. The results demonstrated that the intraocular stimulatory activity for the proliferation of retinal microvascular endothelial cells varied between the different ocular compartments. The mitogenic and migrational activity in vitreous gel was greater than that of either the subretinal or retrohyaloid fluids of the same eye, and the activity of subretinal fluid was intermediate between that of the vitreous gel and the retrohyaloid fluid. There was no significant difference between the activities of the samples from diabetic and non-diabetic eyes.

The exact mechanism of preretinal neovascularisation and its regression after laser photocoagulation is unknown, but these events are thought to be modulated by a 'fine' balance of a variety of growth factors within the eye.[1 2] Since Michaelson first postulated the existence of (and a role for) such biochemical factors in the process of neovascularisation,[3] considerable effort has been expended in identifying the factor or factors responsible for these ocular manifestations.

When comparing the type and number of factors between normal eyes and eyes with vasoproliferative retinopathies the vitreous has proved a convenient source of material since it can be removed easily during surgical procedures and subsequently analysed in the laboratory for its biological activity. However, the vitreous gel (which is usually detached from the retina at the time of vitrectomy)[4] may be some distance from the putative source of the factors in the ischaemic retina. It is therefore possible that the biological activity of the retrohyaloid fluid bathing the ischaemic retina may differ from that in the vitreous gel. Furthermore, eyes with associated tractional retinal detachment can give rise to a fluid filled subretinal space, the fluid of which has been 'conditioned' not only from the ischaemic retina but also from the retinal pigment epithelium. Similar fluid compartments exist in eyes with simple (idiopathic) rhegmatogenous detachment unassociated with neovascularisation but sometimes complicated by non-vascularised periretinal proliferation – 'proliferative vitreoretinopathy' (PVR).[4]

To date vitreous samples from diabetic eyes have been shown to have an increased proliferative activity compared with normal vitreous.[5-9] However, there has been no comparison of the biological activities of fluids from the different intraocular compartments. Thus the aim of this study was to compare the effects of vitreous gel, retrohyaloid fluid, and subretinal fluid from diabetic and non-diabetic eyes on the proliferation and migration of retinal microvascular cells in vitro. Variations in such activity between the different compartments may have a bearing on the pathophysiology and location of the neovascular response.

Materials and methods

ISOLATION OF INTRAOCULAR FLUIDS

Samples of intraocular fluids were obtained at Moorfields Eye Hospital, London during vitrectomy in eyes undergoing repair of retinal detachment, due either to proliferative diabetic retinopathy (13 cases) or rhegmatogenous retinal detachment associated with a degree of proliferative vitreoretinopathy (eight cases). The diabetic patients had either tractional retinal detachment involving the macula or combined traction-rhegmatogenous detachment. All diabetic eyes had previously undergone scatter laser photocoagulation, but the exact extent of this treatment could not be readily quantified.

The non-diabetic patients had rhegmatogenous retinal detachment with signs of proliferative vitreoretinopathy (more than C1).[10] Vitrectomy was performed on these patients either because of the posterior position or large size of the break and/or in order to gain access to the contracted epiretinal membranes. Patients with retinal breaks underwent internal drainage of subretinal fluid during fluid:air exchange.

All diabetic patients had tractional retinal detachments involving the macula with no clinical evidence of intragel, retrohyaloid or subretinal haemorrhages (Table 1). Seven patients had 'pure' traction retinal detachments and six had combined traction-rhegmatogenous retinal detachments. Of the non-diabetic patients, four had proliferative retinopathy requiring epiretinal membrane dissection and four had large and/or posterior retinal breaks requiring internal tamponade. None of the patients studied had clinically recognisable haemorrhage in the vitreous or in the retrohyaloid space.

Undiluted vitreous gel was obtained at the start of the vitrectomy using a 5 ml syringe connected to the vitreous cutter by a short length

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Table 1 Clinical details of patients

	Non-diabetic detachments			Diabetic detachments	
Patient	Type	Duration (weeks)	Patient	Type	Duration (weeks)
1	PVR >D1	12	9	COMB	12
2	PVR >D1	14	10	TRD	24
3	PVR <D1	6	11	COMB	8
4	PVR <D1	8	12	TRD	16
5	PVR <D1	8	13	COMB	12
6	PVR >D1	16	14	TRD	24
7	PVR <D1	12	15	TRD	20
8	PVR <D1	20	16	COMB	12
			17	COMB	14
			18	TRD	28
			19	TRD	20
			20	COMB	8
			21	TRD	24

PVR=proliferative vitreoretinopathy (>D1=greater than stage D; <D1=stages C1 to C4), COMB=combined traction and rhegmatogenous detachment; TRD=traction retinal detachment without retinal breaks

of tubing. The cutter was activated in the mid-vitreous cavity and approximately 0·7 ml of non-haemorrhagic vitreous was aspirated.

Undiluted retrohyaloid fluid was obtained through a small incision in the partially separated posterior hyaloid face. A 20 gauge blunt needle was attached to a 1 ml syringe in which a side opening had been made previously. The end of the needle was inserted through the opening in the hyaloid face and the intraocular infusion of Hartman's solution was started. The increased intraocular pressure allowed the retrohyaloid fluid to enter the collection syringe; 0·7 ml of non-haemorrhagic retrohyaloid fluid was thus obtained.

A volume of 0·3–0·5 ml of subretinal fluid was secured during internal drainage and hydraulic retinal reattachment by fluid-gas exchange using a similar collection system to that employed for recovery of retrohyaloid fluid.

All syringes containing samples were sealed with appropriate stoppers and sent immediately to the laboratory where they were stored at −70°C until required.

PREPARATION OF VITREOUS SAMPLES

Before use the vitreous samples were thawed and liquefied by aspiration through a 27 gauge needle. Owing to the small quantity of material the samples were diluted to an appropriate concentration in the test media and filter sterilised through a 0·22 µm filter (Millipore. USA).

CELL CULTURE

Bovine retinal microvascular endothelial cells were grown in a 1:1 mixture of Dulbecco's modified Eagle's Medium (DMEM) with 7·5% human platelet-poor plasma and pericyte-conditioned medium.[11]

Cultures between the second and third passage were used for all subsequent studies.

PROLIFERATION ASSAYS

A total of 2×10^4 retinal microvascular endothelial cells were seeded into each gelatinised well of 24 well plates (Flow) in DMEM supplemented with 7·5% human platelet-poor plasma. After a period of 24 hours to allow for attachment and initial proliferation the medium was removed and the cells were washed twice with plasma-free DMEM. Each well then received 1 ml of DMEM+7·5% human platelet poor plasma to which had been added 100 µl of liquefied vitreous gel, subretinal fluid, or retrohyaloid fluid. Due to the limited quantity of material available samples were tested either in duplicate or triplicate. Control wells received 1 ml of DMEM containing 100 µl of Dulbecco's phosphate buffered saline without calcium and magnesium (PBSA). After 4 days in the test media cell numbers were determined using a haemocytometer.

Aliquots of cells from each test were stained with trypan blue in order to determine any cytotoxic effect.

MIGRATION ASSAYS

Migration assays were undertaken on representative samples as described by Singh *et al* using 48 well modified Boyden chambers.[12] Briefly, the lower wells were filled with test media consisting of 100 µl/ml of either liquefied vitreous gel, subretinal fluid or retrohyaloid fluid added to plasma-free DMEM. Each test medium type was added to six wells. In control wells the intraocular fluid was substituted with an equivalent volume of PBSA. The wells were then overlaid with a type 1 collagen (Ethicon) coated polycarbonate membrane with 10 µm pores and the chambers assembled. Upper wells were filled with a suspension of retinal microvascular endothelial cells in plasma-free medium at a cell density of 10^9/l. The chambers were then incubated for 6 hours at 37°C. The membrane was removed, fixed in methyl alcohol and stained with modified Wright's stain. The number of cells which had migrated through the polycarbonate membrane were counted after the non-migrated cells had been wiped from the top surface. Cell nuclei in 10 high power fields (×40) were counted in each well.

PROTEIN ASSAYS

The protein content of the samples was determined using the Biorad Coomassie blue assay kit according to the manufacturers instructions.

LACTATE MEASUREMENTS

Due to the possibility of dilution of the retrohyaloid and subretinal samples by contamination with Hartman's buffer during infusion at surgery, levels of lactate (a major constituent of Hartman's) were measured in the Department of Clinical Biochemistry, Manchester Royal Infirmary.

STATISTICS

All data from the proliferation and migration experiments are expressed as mean (SD). Where possible the statistical significance of the data from the different samples was examined by analysis of variance.

Table 2 The effect of vitrectomy samples from diabetic and non-diabetic patients on the proliferation of retinal capillary endothelial cells

Patient no	C	V	S	R	Result[b]
Non-diabetic patients					
1	26·0 (2·1)[a]	38·0 (4·0)[a]	23·0 (1·8)[a]	–	V>S
2	26·0 (2·1)	42·0 (5·2)	36·0 (3·7)	–	V=S
3	26·0 (2·1)	49·4 (6·1)	34·0 (4·3)	–	V>S
4	26·0 (2·1)	43·4 (4·7)	–	28·0 (2·4)[a]	V>R
5	26·0 (2·1)	28·0 (3·3)	–	–	
6	26·0 (2·1)	47·0 (4·5)	39·4 (3·9)	–	V=S
7	26·0 (2·1)	27·4 (2·5)	–	–	
8	26·0 (2·1)	34·0 (2·9)	30·0 (3·0)	–	V=S
Diabetic patients					
9	26·0 (2·1)	26·6 (2·8)	–	32·0 (2·6)	R=V
10	26·0 (2·1)	38·0 (2·7)	10·0 (4·1)	28·0 (1·9)	V>R>S
11	26·0 (2·1)	50·0 (6·1)	–	31·0 (2·4)	V>R
12	26·0 (2·1)	49·0 (4·3)	31·4 (2·0)	–	V>S
13	26·0 (2·1)	50·6 (4·5)	50·0 (3·5)	29·2 (1·7)	V=S>R
14	26·0 (2·1)	39·4 (2·6)	–	38·6 (2·4)	V=R
15	26·0 (2·1)	58·6 (6·8)	–	31·4 (2·5)	V>R
16	26·0 (2·1)	35·4 (3·3)	2·6 (1·2)	24·6 (1·8)	V>R>S
17	26·0 (2·1)	44·0 (3·8)	37·0 (4·8)	28·0 (2·2)	V=S>R
18	26·0 (2·1)	57·0 (4·6)	–	34·0 (2·1)	V>R
19	26·0 (2·1)	50·0 (5·4)	–	27·0 (2·2)	V>R
20	26·0 (2·1)	37·0 (3·2)	33·4 (2·7)	8·0 (5·8)	V>S>R
21	26·0 (2·1)	42·5 (3·1)	–	31·0 (2·1)	V>R

[a] Standard deviations (SD).

[b] Statistical comparisons between different samples from the same eye ($p<0·05$ is considered significant)

The mean number of cells ($\times 10^3$) is given in each column C=control, V=vitreous; S=subretinal fluid; R=retrohyaloid fluid

Results

PROLIFERATION

Samples of vitreous gel from 12 of the 13 diabetic patients significantly stimulated the proliferation of retinal microvascular endothelial cells when compared with the control basal media (Table 2). By contrast 11 of the 12 retrohyaloid samples had proliferative activity similar to or only slightly more than that of the control basal media; the remaining sample showed less proliferative activity. Furthermore, the retrohyaloid fluid from 10 of 12 diabetic eyes exhibited significantly less mitogenic activity when compared with their respective vitreous gel samples. The results for the subretinal fluid were highly variable with some samples showing higher mitogenic activity than the control basal medium and others exhibiting less activity (Table 2). None of the subretinal fluid samples demonstrated greater proliferative activity than their respective vitreous gel samples. No cytotoxicity was observed in any of the test media using the trypan blue exclusion test but in some instances in which the final cell numbers were less than those in the basal medium, unstained cells could be observed floating in the medium (patients 10, 16, and 20).

Results from the non-diabetic samples were inconsistent (Table 2). The vitreous gel stimulated cell proliferation in six of the eight cases and had no effect in the other two. The one retrohyaloid fluid sample that was obtained had lower mitogenic activity than the corresponding vitreous gel but the same activity as the control basal medium. The subretinal fluid samples exhibited either similar or less activity than their corresponding vitreous samples.

Table 3 The effect of vitrectomy samples from diabetic and non-diabetic patients on the migration of retinal capillary endothelial cells

Patient no	0% DMEM	V	S	R	7·5% DMEM	Result[b]
Non-diabetic patients						
1	10·7 (1·6)[a]	20·2 (1·3)[a]	8·1 (0·6)[a]	–	49·7 (5·2)[a]	V>S
2	10·7 (1·6)	43·6 (3·4)	42·2 (2·8)	–	49·7 (5·2)	V=S
3	10·7 (1·6)	15·7 (1·0)	25·1 (1·8)	–	49·7 (5·2)	S>V
4	10·7 (1·6)	22·2 (1·7)	–	9·9 (0·5)	49·7 (5·2)	V>R
Diabetic patients						
9	10·7 (1·6)	8·1 (0·4)	–	9·3 (0·5	49·7 (5·2)	V=R
13	10·7 (1·6)	24·8 (1·6)	8·1 (0·7)	11·4 (0·9)	49·7 (5·2)	V>R>S
15	10·7 (1·6)	27·7 (2·1)	–	3·1 (0·2)	49·7 (5·2)	V>R
17	10·7 (1·6)	17·9 (0·8)	15·5 (1·1)	12·6 (0·6)	49·7 (5·2)	V>S=R
18	10·7 (1·6)	42·9 (3·7)	–	23·3 (2·0)	49·7 (5·2)	V>R

[A] Standard deviations (SD)

[b] Statistical comparisons between different samples from the same eye ($p<0·05$ is considered significant).

The mean number of cells per high power fields is given in each column. V=vitreous, S=subretinal fluid, R=retrohyaloid fluid

MIGRATION

With the exception of one diabetic vitreous sample (patient 9) all the vitreous samples tested stimulated endothelial cell migration when compared with serum free media (Table 3). Again with the exception of patient 9 cell migration was greater in the vitreous gel samples than the corresponding retrohyaloid fluids. In four of the six retrohyaloid samples cell migration was similar to that observed with basal medium, while one had increased migration and the other decreased migration compared with the control medium. The capability of subretinal fluid samples to promote cell migration was variable; some samples stimulated cell migration while others gave values similar to that of the baseline control.

PROTEIN CONCENTRATIONS

The protein concentrations of the vitreous samples, both diabetic and non-diabetic, ranged from 175 to 2300 mg/ml (Table 4). In 10 of 13 diabetic patients the protein concentrations in the retrohyaloid fluids were less than the concentrations in the corresponding vitreous gel samples. In only one patient (patient 10) was the protein concentration of the retrohyaloid fluid greater than that in the corresponding vitreous gel sample. The protein concentrations of the subretinal fluids were variable with values ranging from 20 to 2550 mg/ml. In general the

Table 4 Protein concentration (mg/l) in vitrectomy samples from diabetic and non-diabetic patients

Patient no	V	S	R	Result[a]
Non-diabetic patients				
1	2068	20	–	V>S
2	1860	2240	–	S>V
3	1550	1843	–	S>V
4	850	–	135	V>R
5	255	–	–	
6	2375	2550	–	V=S
7	550	–	–	
8	1430	2060	–	S>V
Diabetic patients				
9	700	–	205	V>R
10	175	2500	445	S>R>V
11	1410	–	860	V>R
12	1460	50	–	V>S
13	1640	690	690	V>S=R
14	2300	–	2350	V=R
15	1850	–	50	V>R
16	790	2550	20	S>V>R
17	1700	895	420	V>S>R
18	2135	–	1650	V>R
19	2035	–	1760	V>R
20	1110	850	345	V>S>R
21	2000	–	90	V>R

[a] Statistical comparisons between different samples from the same eye ($p<0·05$ is considered significant)

V=vitreous; S=subretinal fluid, R=retrohyaloid fluid

Table 5 Comparison of proliferative activity, migratory activity and protein content of diabetic and non-diabetic samples

Patient no	*Proliferative activity*	*Migratory activity*	*Protein content*
Non-diabetic patients			
1	V>S	V>S	V>S
2	V=S	V=S	S>V
3	V=S	S>V	S>V
4	V=R	V>R	V>R
5	–	–	–
6	V>S	–	V=S
7	–	–	–
8	V>S	–	S>V
Diabetic patients			
9	V=R	V=R	V>R
10	V>R>S	–	S>R>V
11	V>R	–	V>R
12	V>S	–	V>S
13	V=S>R	V>S>R	V>S=R
14	V=R	–	V=R
15	V>R	V>R	V>R
16	V>R>S	–	S>V>R
17	V=S>R	V>S=R	V>S>R
18	V>R	V>R	V=R
19	V>R	–	V>R
20	V=S>R	–	V>S>R
21	V>R	–	V>R

V=vitreous, S=subretinal fluid, R=retrohyaloid fluid. The columns show the statistical comparisons between different samples from the same eye ($p<0\ 05$ is considered significant).

protein content of the subretinal fluid was higher than that of the respective retrohyaloid fluid but no correlation could be made with the vitreous gel samples.

When comparing the proliferative activity, migratory activity and protein content of the intravitreal samples the correlation between the different parameters was positive overall for eight out of 13 patients (diabetic and non-diabetic) and for 10 out of 13 patients when comparing vitreous with retrohyaloid fluid (Table 5). No correlation could be found for the subretinal fluid samples.

LACTATE LEVELS

In order to determine if the low biological activity in the retrohyaloid and subretinal fluids was due to dilution by Hartman's buffer during infusion at surgery, lactate levels were measured in representative samples of the different fluids. The lactate concentration in Hartman's buffer was 29 mmol/l. The lactate levels in the vitreous gel ranged from 3·0 to 5·8 mmol/l while they were significantly greater ($p<0{\cdot}005$) in the retrohyaloid fluid ranging from 5·1 to 9·2 mmol/l (Table 6). If the differential between the lactate content in the vitreous and the retrohyaloid fluid reflected contamination by Hartman's buffer the dilution factor would range from 4·8 to 12%. The lactate levels in the two subretinal fluid samples tested (9·7 and 11·2 mmol/l) were higher than those in either the vitreous gel samples or the retrohyaloid fluids.

Table 6 Lactate levels in vitrectomy samples from diabetic and non-diabetic patients

Patient no	*V*	*S*	*R*
Non-diabetic patients			
1	5·8	11·2	–
3	5 8	9·7	–
4	4 4	–	–
Diabetic patients			
9	5·7	–	9·2
13	3 0	–	5 1
14	5·0	–	8 4
18	5·4	–	6 8
20	3 0	–	5·1
(Hartman's buffer=29 mmol/l)			

Values are given as mmol/l of lactate V=vitreous; S=subretinal fluid; R=retrohyaloid fluid

Discussion

This study demonstrates that intraocular stimulatory activity varies between the different intraocular compartments in eyes undergoing vitrectomy for retinal detachment. The mitogenic and migrational activity in vitreous gel was greater than that of either the subretinal or retrohyaloid fluids of the same eye, while the activity of subretinal fluid was generally intermediate between that of the vitreous gel and the retrohyaloid fluid. An obvious explanation for the lower activities in retrohyaloid and subretinal fluids compared with vitreous gels is that these samples may be diluted by Hartman's solution used as the infusion during surgery. However this was not the case since the slight increase in lactate levels in samples taken after Hartman's infusion commenced at surgery was insufficient to account for the large differences in biological activity between the different intraocular compartments in individual eyes. The levels of lactate in the vitreous gel were similar to those previously reported for normal human vitreous[13] (even though lactate levels are known to increase in certain disease conditions).[14] Thus if the increase in lactate observed in the retrohyaloid and subretinal fluids is related to the disease process and not to the infusion fluid the differences in activity would be much greater. Whilst the protein concentrations in the vitreous gel and retrohyaloid samples were highly variable between different eyes the general trend was for the protein content of the retrohyaloid fluid to be lower than that of the vitreous gel from the corresponding eye. The highly variable protein content of the subretinal fluid samples could be explained by the duration of the detachment.

Interestingly there was no significant difference between the activities of the samples from diabetic and non-diabetic patients. This is contrary to previous studies which have shown that the mitogenic activity of intraocular fluid is raised in diabetic eyes compared with non-diabetic eyes.[5 6 9] One explanation is that the non-diabetic patient group had active PVR and stimulatory activity would be expected to be present. However the factors present may differ between the two groups. Campochiaro *et al* demonstrated that the stimulation of retinal pigment epithelial migration by vitreous aspirates from patients with PVR was greater than that in aspirates from macular puckers and uncomplicated detachments.[7] This supports the possibility that the non-diabetic PVRs are rich in stimulatory activity.

The reason why the biological activities were greatest in the vitreous gel is unclear. Although many of the stimulatory factors are thought to orginate from the retina other sources during retinal pathologies could include leakage from preretinal vessels and the release of factors from cells in or associated with the preretinal vessels growing in the cortical gel.[1 2] The higher levels of activity in the vitreous gel compared with the retrohyaloid and subretinal compartments could be explained in a number of ways. Firstly, the molecular sieve properties of the gel could trap factors within the vitreous and thus cause the build up of a concentration gradient.[15] Secondly, since many growth factors are bound to extracellular matrix components[16] it is possible that retina/RPE derived growth factors become bound to components in the vitreous gel and thus reach a high concentration. Thirdly, the balance between stimulatory and inhibitory activity in the vitreous may be altered during pathological conditions. The results presented do not indicate if the greater biological activity in the vitreous is due to increased stimulatory activity or a decrease in inhibitory activity. Fourthly, the lower activities in the retrohyaloid and subretinal fluids could be explained by the fact that these fluids are closer to retinal cells that consume growth factors than is the vitreous.

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Blood-ocular barrier permeability in monkeys

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Abstract

The permeability of the blood-ocular barrier was investigated in five monkeys using vitreous fluorophotometry (VFP). Inward permeability (P_{in}) of the blood-retinal barrier was calculated by a computer simulation method. Kinetic VFP was performed after intravitreal injection of fluorescein (F) or fluorescein monoglucuronide (FG). The estimated mean value of P_{in} ($\times 10^{-6}$ cm/min) was 4·8 (SD 1·2). The mean rates of loss (per hour) of F from the anterior chamber (K_a) and the vitreous (K_v) were 0·11 (SD 0·01) and 0·13 (SD 0·03), respectively, which were approximately three and four times greater than those of FG (0·04 (SD 0·01) and 0·03 (SD 0·01), respectively). Probenecid administered intraperitoneally decreased both the K_a and the K_v of F significantly but had no effect on the K_a or the K_v of FG, suggesting that F was excreted from the eye with the aid of the active transport mechanism. The results of comparative studies of the rates of loss of F from the anterior chamber (K_a) and from the vitreous (K_v) suggested that active transport was more predominant in the blood-retinal barrier than in the blood-aqueous barrier.

Studies performed using vitreous fluorophotometry (VFP) have demonstrated the presence of certain mechanisms in the blood-ocular barrier (BOB), such as the inhibition of intraocular penetration of some substances from the blood and the excretion of some substances from the eye via active transport.[1] However, little has been learned about the physiological mechanism of active transport in the BOB because the metabolism of fluorescein-Na (F) used in VFP interferes with the determination of this mechanism. Systemically administered F has been shown to be metabolised rapidly to fluorescein monoglucuronide (FG)[2] and that it is more difficult for FG than F to undergo active transport.[3 4] Thus, when the intraocular active transport function is studied using VFP, the intraocular kinetics of both F and FG should be followed.[5 6]

Rabbit eyes have been used widely for the study of the intraocular active transport function,[1 3 4 7] but the structure of the retinal vasculature in rabbits differs markedly from that in humans. Therefore, it is difficult to extrapolate the results obtained in rabbits to humans. Moreover, the direct injection of F into the human vitreous is restricted. In this study we used the monkey eye to analyse the permeability function of the BOB since it resembles the human eye in anatomy and retinal vasculature. This function was classified into inward and outward permeabilities by monitoring the fluorescence kinetics.

To analyse the inward permeability (P_{in}) of the BOB, particularly of the blood-retinal barrier (BRB), F was injected intravenously, and a P_{in} coefficient of the BRB was calculated using VFP and a computer simulation method.[5 8] In this study, the outward permeability (P_{out}) of the BOB was estimated by injecting F or FG into the vitreous and determining changes in the concentration periodically using VFP. Our study demonstrated that the P_{in} of the BRB in the monkey eye is nearly equivalent to that in the human eye, which allowed us to speculate on the homeostasis of the human vitreous in relation to BOB function.

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Materials and methods

MATERIALS

Ten eyes of five adult cynomolgus monkeys (all male) weighing 3·0–5·0 kg were used. The following experiments were performed under a light anaesthesia induced by an intramuscular injection of ketamine hydrochloride and pentobarbitone sodium.

REFRACTION MEASUREMENTS

Both pupils of each monkey were dilated with 0·5% phenylephrine hydrochloride and 0·5% tropicamide. The dioptric power (D) of each eye was measured by refractometer (Ophthalmometer, Zeiss Jena, Germany), and the optical elements such as anterior chamber depth, lens width, and vitreous cavity length were determined using A-mode ultrasonography (Ophthalmoscan 200, DBR Sonometrics, Lake Success, NY, USA).

VITREOUS FLUOROPHOTOMETRY

After dilatation, the eyes were evaluated further by indirect ophthalmoscopy. No fundus abnormalities were found. The vitreous body of each eye was examined using a slit-lamp with an aspheric +58·6 D lens (El Bayadi-Kajiura).[9] No vitreous abnormalities, such as liquefaction, lacuna formation, or any type of posterior vitreous detachment were apparent.

VFP then was performed on all 10 eyes. The fluorophotometer used in this study has been described in detail elsewhere.[10 11] In short, a modified Haag-Streit model 360 slit-lamp was used to record equivalent F concentration profiles in the ocular media. The angle between illumination and measuring light paths was 14 degrees, and the beam dimensions at the focal plane in air were 3 mm×150 μm and 2·8 mm×150 μm, respectively. The meter readings of this system were linearly related to the F concentrations in a range from $7{\cdot}0\times10^{-11}$ to $8{\cdot}0\times10^{-7}$ g/ml.

After topical anaesthesia with 0·4% benoxynate hydrochloride, a low vacuum contact lens

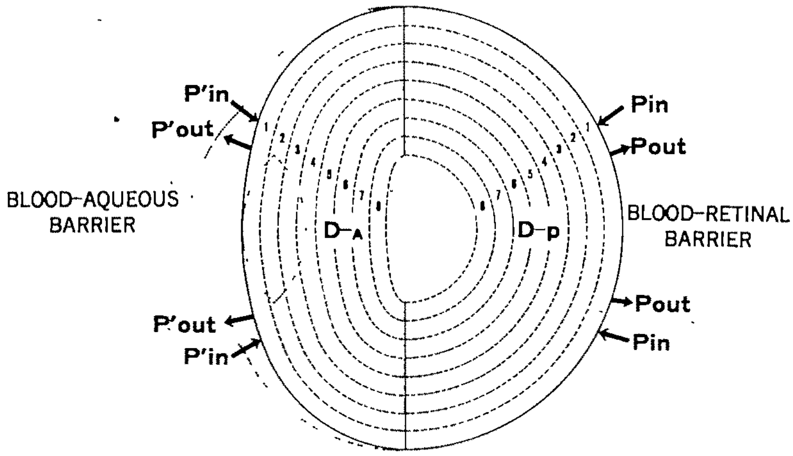

Figure 1 Schematic illustration of the simulation model.

was placed on the cornea using methylcellulose solution. Measurements were taken before (baseline) and 60 minutes after antecubital vein injection of 10% F (Fluorescite, Alcon, Fort Worth, TX, USA) at a dose of 7 mg/kg body weight.

To determine the concentration of protein-unbound free F (PUF) in plasma, blood was sampled from the antecubital vein on the side opposite to the dye injection at 10 and 65 minutes following fluorescein injection by methods previously described.[12]

ESTIMATION OF INWARD PERMEABILITY OF THE BLOOD-RETINAL BARRIER

To estimate the P_{in} of the BRB with our computer simulation technique,[5 8] we adopted the values at 14 dispersed sampling points, utilising serial VFP measurements. The value for the anterior vitreous was derived from seven points 0·4 mm apart starting from a point 2·0 mm posterior to the centre of the crystalline lens; the value for the posterior vitreous was derived from seven points 0·4 mm apart between the 2·4 and 4·8 mm anterior points from the retinal surface. All these VFP readings were corrected for the baseline value.

The model we used for computer simulation of intraocular F kinetics has been described in detail.[5 8] Briefly, the eyeball is divided into anterior and posterior segments (Fig 1). The posterior part is assumed to be ellipsoid. The length of the ellipsoid axis can be altered according to the actual length of the vitreous cavity obtained from A-mode ultrasound measurement. The anterior and posterior parts were divided into eight compartments, each consisting of a thin shell. The thickness of each shell is 0·8 mm for the money eye. In the posterior half, P_{in} and P_{out} are the two parameters of the BRB permeability coefficient, and *D-p* represents the dye diffusion coefficient in the posterior vitreous cavity. Similar parameters in nature were used for the anterior part of the eye. Based on this model, dye kinetics in the vitreous cavity were simulated, and P_{in} and *D-p* values were estimated for each eye.

Table 1 Refraction and optical element measurements (n=10)

Parameter	*Range*	*Mean (SD)*
Dioptric power (D)	−0·5–0	−0·3 (0·3)
Anterior chamber depth (mm)	2·50–3·36	2·93 (0·33)
Lens width (mm)	3 15–3·65	3·40 (0·15)
Vitreous cavity length (mm)	11·20–14·75	12·24 (1·47)
Axial length (mm)	16·80–21·50	18·57 (1·81)

CHANGES OF INTRAOCULAR FLUORESCENCE FOLLOWING INTRAVITREAL INJECTION OF FLUORESCEIN OR FLUORESCEIN MONOGLUCURONIDE

One month after the previous experiment, indirect ophthalmoscopy revealed no fundus abnormalities. Intraocular autofluorescence was then measured by fluorophotometry. Ten µl of a 1 mmol solution of F, prepared in isotonic phosphate buffered saline (pH 7·4), was injected directly into the centre of the vitreous cavity through a 30 gauge needle placed on the pars plana in the right eye of the monkeys. The left eye was injected in the same manner with the same amount and concentration of FG (synthesised by Chugai Pharmaceutical Co, Ltd, Tokyo), prepared in isotonic phosphate buffered saline. Its purity was specified by the manufacturer to be 99·17% FG and 0·21% F. Intraocular fluorescence was measured 6, 8, 10, 12, and 24 hours after injection.

EFFECTS OF INTRAPERITONEAL INJECTION OF PROBENECID

Two months following the intravitreal injection, the subjects were examined to ensure that no fundus or vitreous abnormality had developed. Probenecid (Sigma Chemical Co, St Louis, MO, USA), a known inhibitor of active transport of F from the eye,[13] then was given intraperitoneally (150 mg/kg) to the five monkeys, twice, just before and 6 hours following intravitreal injection of F or FG. Intraocular fluorescence again was measured by VFP.

DATA ANALYSIS

The data were analysed using standard statistical methods. Student's unpaired *t* tests were used to compare groups. Paired *t* tests were performed for paired parameters. Differences were considered significant when the probability value indicated a chance of random occurrence of less than 5%.

Results

REFRACTION AND OPTICAL ELEMENTS

The values of the refraction and optical elements are shown in Table 1. The refraction ranged from −0·5 to 0 D and was emmetropic.

Mean axial length was 18·57 mm (SD 1·81), corresponding to ~78% of that of the human eye.[14] The mean ratio of each optical element to axial length in monkeys was 0·16 for anterior chamber depth, 0·18 for lens width, and 0·66 for vitreous cavity length. These ratios of each element to the axial length in monkeys' eye was similar to that obtained from the human eye (0·15, 0·18, and 0·68, respectively).[14]

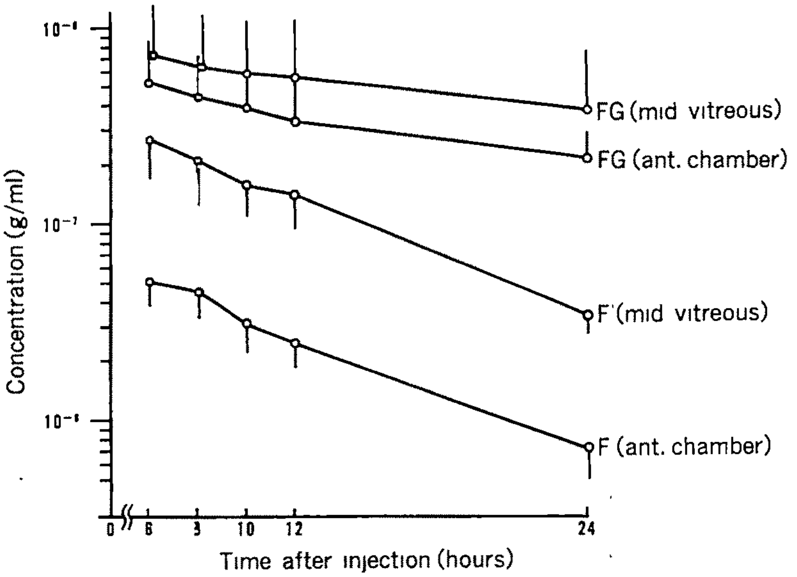

Figure 2 Time courses of concentration changes in the anterior chamber and vitreous following intravitreal injection of fluorescein and fluorescein monoglucuronide.

INWARD PERMEABILITY OF THE BLOOD-RETINAL BARRIER

The mean estimated P_{in} value by the computer simulation method was $4{\cdot}8\times10^{-6}$ cm/min (SD 1·2).

CHANGES OF INTRAOCULAR FLUORESCENCE FOLLOWING INTRAVITREAL INJECTION OF F OR FG

The time course of intraocular fluorescence measured following intravitreal injection of F or FG was studied with emphasis on two values: the anterior chamber value represented by the central value of the anterior chamber, and the vitreous value represented by the value in the vitreous 6 mm anterior to the retina (Fig 2). Values were displayed by converting them to actual concentrations of F or FG, which were based on each fluorescence intensity. The concentration of F in the anterior chamber and vitreous decreased rapidly with time compared with the FG concentration in those sites. Furthermore, the F concentration in the mid-vitreous showed consistently higher levels than in the anterior chamber in contrast to the FG concentration, which showed only a slightly higher level in the mid-vitreous.

The rates of loss (per hour) of F and FG from the anterior chamber (K_a) and vitreous (K_v) were calculated using fluorescence values obtained 12 and 24 hours following intraocular injection (Table 2). To compare the rates for F and FG, we determined K_a(F)/K_a(FG) and K_v(F)/K_v(FG). The mean ratios were 2·9 (SD 0·5) and 4·7 (SD 1·4), respectively; the difference was statistically significant ($p<0{\cdot}05$).

Table 2 Rate of loss (per hour) from anterior chamber (K_a) and vitreous (K_v) following intravitreal injection of F or FG (n=5)

	Without probenecid		*With probenecid*	
	F	*FG*	*F*	*FG*
K_a	0·11 (0·01)[a]	0·04 (0 01)[a]	0·09 (0·04)[a]	0·04 (0·01)[a]
K_v	0·13 (0·03)	0·03 (0 01)	0·05 (0·03)	0·03 (0·01)

F=fluorescein, FG=fluorescein monoglucuronide; K_a=rate of loss from anterior chamber; K_v=rate of loss from vitreous.
[a]Standard deviation (SD)

EFFECTS OF INTRAPERITONEAL INJECTION OF PROBENECID

Intraperitoneal administration of probenecid, an inhibitor of active transport of F from the eye, significantly decreased the mean values (per hour) of K_a and K_v of F to 0·09 (SD 0·04) ($p<0{\cdot}05$) and 0·05 (SD 0·03) ($p<0{\cdot}05$), respectively (Table 2), compared with the values without probenecid. The values for K_a and K_v of FG (0·04 (SD 0·01) and 0·03 (SD 0·01), respectively), however, remained unchanged with the administration of intraperitoneal probenecid (Table 2).

Discussion

Our present study revealed that refraction of the monkey eyes was emmetropic and that the structure of monkey eyes, based on the ratio of each optical element to the axial length, was similar to human eyes. P_{in} ($\times10^{-6}$ cm/min) of the monkey eyes was 4·8 (SD 1·2), which is ~77% of the value in humans (6·2 (SD 1·8)).[8] These findings allow us to state that passive transport functions similar to those in human eyes exist in the BRB of monkeys.

Cunha-Vaz and Maurice[1] reported that F infused into the rabbit vitreous cavity was excreted via the BRB by active transport into the bloodstream. Active transport function in the BOB has also been analysed.[3-6, 15-21] We found that the K_v (per hour) of FG was nearly the same as that of sucrose (K_v=0·04)[22] or gentamicin (K_v=0·035), which was found to be excreted from the eye only by passive transport.[23] This, together with the fact that the K_v of F is about four times greater than the K_v of FG in the vitreous, allows us to assume that F is excreted from the eye mainly by active transport in the monkey eye. Further, intraperitoneal administration of probenecid, an inhibitor of active transport, caused a decrease in K_a (per hour) and K_v of F but had no measurable effect on K_a and K_v of FG. These results strongly suggest that F and FG are excreted from the eye mainly by active and passive transport, respectively.

The value of K_v(F)/K_v(FG) was found to be greater than that of K_a(F)/K_a(FG), and the difference was statistically significant. This finding, together with the K_v values obtained from the kinetics of fluorescence in the mid-vitreous (which is surrounded by the retina and thus reflects the retinal dye excretion), contributes to the assumption that intraocular active transport is greater in the BRB than in the blood-aqueous barrier. This result agrees with Miyake's[24] who used enucleated human eyes to study the active transport of F from the vitreous cavity to the bloodstream in vitro. He found that the retina represented the main region of blood-ocular active transport (76% of the active transport rate).

The value of P_{in} of the BRB of the monkey was determined to be nearly equivalent to that of the human eye. This monkey model was extremely useful because it allowed us to evaluate direct infusion of F or FG into the eye, which could not be performed in humans. Using direct infusion, we observed the presence of an active transport system and some of its characteristics in the BOB. We speculated that the active transport system plays an important role in maintaining vitreous homeostasis not only in the monkey eye but also in the human eye. Our findings may provide important clues for understanding the function of the BRB in the human eye.

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A comparison of 141 polymacon (Iogel) and 140 poly(methyl methacrylate) intraocular lens implants

K J Lowe, D L Easty

Abstract

In a prospective controlled trial 290 consecutive patients were randomly allocated a polymacon or a poly(methyl methacrylate) (PMMA) intraocular lens. Early Treatment of Diabetic Retinopathy Study (ETDRS) acuity charts gave similar results with both lenses. However Pelli-Robson contrast sensitivity charts gave a better result with PMMA lenses. Polymacon lenses appeared to remain free of any adhesions after implantation raising the question of long term stability. Four patients experienced problems related to this, three involved total lens dislocation. Seven patients developed early 'fibrin' membranes coating the polymacon lens, of which three were florid.

Current intraocular lenses are relatively safe and provide good visual results. Modifications, new designs, and/or materials appear frequently. New is not necessarily better and apparently useful properties may also have disadvantages.

Polymacon (polyhema) is known to be less damaging to the corneal endothelium and less likely to cause inflammation in the eye due to its hydrophilic nature.[1] It is a flexible material allowing the lens to be folded. All previous reports mentioned refer to the PC12 (12 mm long) polymacon lens. Initial reviews of this lens have been favourable.[2-4] There have however been several reports noting poor centration and even dislocation.[4 8 9] Some concern was also expressed about the positioning of the lens in the eye though it was felt that placement in the bag would overcome this.[6] A trial of several types of soft lens including polymacon concluded that caution was necessary in recommending soft lenses at present.[10]

The 1988 American Society of Cataract and Refractive Surgery (ASCRS) survey showed that PMMA was used by 95% of its members, only 2% used polymacon.[11] A survey by the European Intraocular Lens Implant Council (EIIC) covering 14 countries showed that on average 98·2% used PMMA lenses and only 1·2% used polymacon.[12] The use of polymacon lenses varied from 0–6% by country. However due to the low response rate and the limitations of the sample population this survey may not be representative. We compared a one piece polymacon lens (Alcon Iogel PC1103, 11·3 mm long) with a standard PMMA posterior chamber lens with poly(propylene) loops (Pharmacia 150A J-LP UV).

Materials and method

A total of 290 patients were randomly allocated a polymacon or PMMA intraocular lens before being seen in a preoperative assessment clinic.

The operation was a standard endocapsular cataract extraction with planned 'in the bag' placement of the lens. All operations were performed by the same surgeon using posterior peribulbar anaesthesia. The only difference in operative technique between the two groups was the routine use of a viscoelastic material (Healon) with PMMA lenses. Lens placement was not routinely verified postoperatively.

Patients were reviewed at 2, 8, and 16 weeks postoperatively. ETDRS charts were used to measure acuity since they are easier to analyse for statistical purposes due to their regular progression in letter size and simple logarithmic scoring system.[13] Visual results relate to acuity with spectacle correction if prescribed. However 40 patients in the polymacon group and 32 patients in the PMMA group chose not to wear spectacles for distance. Their uncorrected distance acuity is included since we felt this was a more realistic assessment of their everyday visual performance. Contrast sensitivity was also measured using the Pelli-Robson chart at 3 metres which gave further information on the quality of vision.[14]

Results

Operations were performed on 290 consecutive patients. Three died and six defaulted leaving 141 patients in the polymacon group and 140 in the PMMA group at 16 weeks.

The composition of both groups was similar by age and sex. The PMMA group had a mean age of 73·59 years (SD 8·03) and a male to female ratio of 52:88. The polymacon group had a mean age of 73·11 years (SD 8·28) and a male to female ratio of 55:86.

In terms of ETDRS acuity results were similar particularly when patients with pre-existing pathology such as age-related maculopathy, diabetic maculopathy, and pathological myopia were excluded (Table 1). The PMMA group had a mean acuity of 0·26 (SD 0·14) and the polymacon group a mean acuity of 0·28 (SD 0·15). A *t* test comparing polymacon and PMMA groups showed no significant difference ($p=0·14$).

Excluding pre-existing pathology as before the PMMA group had a mean contrast sensitivity for the frequency range 3–5 cycles/degree of 1·21 (SD 0·22) (Table 2). The polymacon group had a mean of 1·12 (SD 0·23). A *t* test showed the PMMA group to be significantly better ($p<0·0001$).

A list of problems associated with both lens types is given in Table 3. Moderate and severe examples of a 'fibrin' membrane are shown in Figs 1 and 2).

Of the 141 polymacon and 140 PMMA lenses 15 and 13 respectively caused some difficulty

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*Table 1 ETDRS acuity is as good as or better than increment**

ETDRS (log)	*PMMA*		*Polymacon*	
	All	*Corrected*	*All*	*Corrected*
0·0 (6/6)	8	8	6	6
0·1	17	17	18	18
0·2 (6/9)	38	38	31	31
0·3 (6/12)	33	33	39	39
0·4	18	17	18	15
0·5 (6/18)	12	8	10	7
0·6 (6/24)	6	3	5	4
0·7	3	0	5	2
0·8	0	0	4	1
0·9	0	0	1	0
1·0 (6/60)	1	0	0	0
1·1	3	0	1	0
CF	1	0	2	0
PL	0	0	1	0
Total	140	124	141	123

CF=counting fingers; PL=perception of light.
*Measured on an open ended logarithmic scale. Approximate Snellen acuity is given in brackets for comparison. Patients with pre-existing pathology are excluded in the corrected group.

Table 2 Contrast sensitivity measured using the Pelli-Robson chart at 3 m

Pelli-Robson (log)	*PMMA*		*Polymacon*	
	All	*Corrected*	*All*	*Corrected*
0·00	1	0	3	0
0·15	2	1	1	0
0·30	0	0	0	0
0·45	1	0	3	2
0·60	2	1	1	1
0·75	8	2	17	10
0·90	7	2	13	11
1·05	36	36	34	34
1·20	26	26	15	15
1·35	28	28	36	36
1·50	10	10	3	3
1·65	5	5	0	0
Total	126	111	126	112

This is measured on a logarithmic scale, 0·0 approximates to 100% contrast and 2·0 is 1% contrast. Patients with pre-existing pathology are excluded in the corrected group. The first 14 PMMA and 15 polymacon patients did not have this test.

Table 3 Problems associated with PMMA and polymacon lenses

	PMMA	*Polymacon*
Marked pigment release	1	5
Uveitis	4	5
'Fibrin' membrane	1	7
Cystoid macular oedema	0	1
Unsatisfactory position	2 (1)	5 (2)
Dislocation	0	3
YAG capsulotomy	11	13

Figures in brackets noted at time of operation.

during implantation. Three operations in the polymacon group and five in the PMMA group were considered technically difficult. It was not necessary to change the type of lens implant at operation. No capsules were ruptured in the polymacon group and three were ruptured in the PMMA group, but posterior chamber lens implantation was still possible.

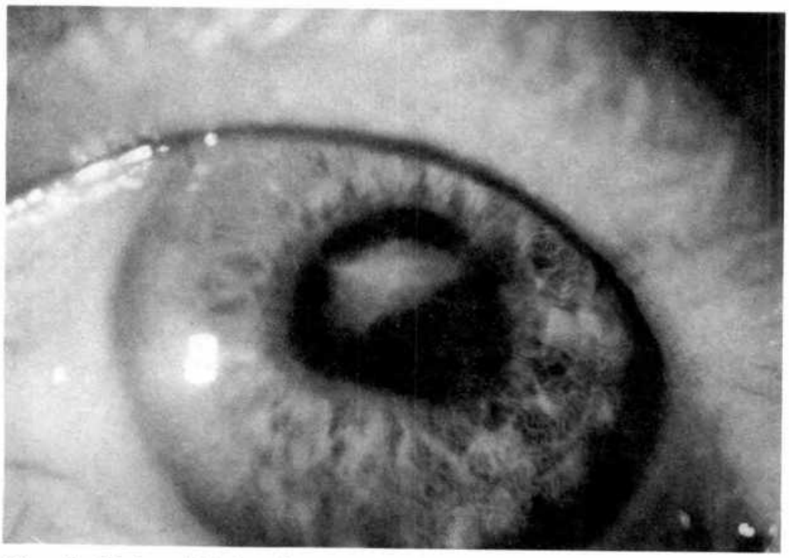

Figure 1 Moderate 'fibrin' membrane associated with a polymacon lens.

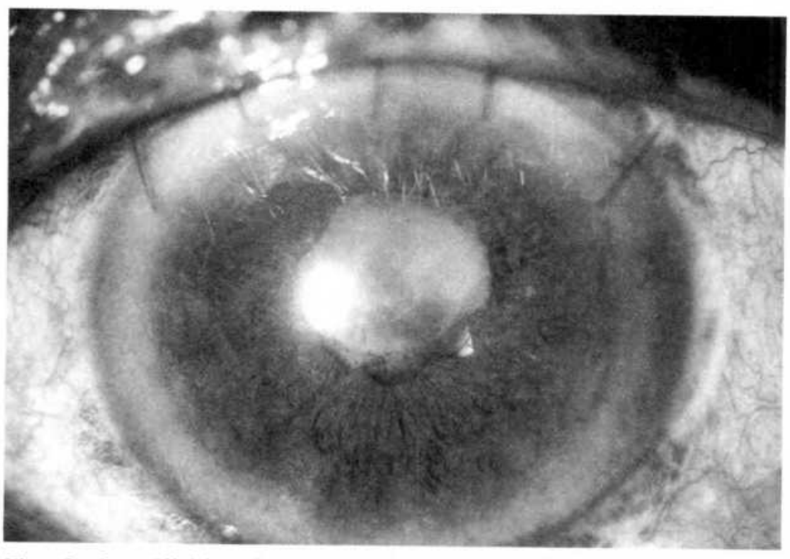

Figure 2 Severe 'fibrin' membrane associated with a polymacon lens.

Discussion

We were surprised to find a significant difference in contrast sensitivity. The visible transmission for polymacon lenses is 95% (manufacturer's figures). Polymacon lenses do have a slightly milky appearance when viewed by slit-lamp, which may be relevant. Further investigation of the contrast sensitivity function in patients with this type of lens is required. Resolution alone is no longer sufficient when considering the properties of an intraocular lens. A graph of the modulation transfer function of the lens would provide important additional information.

The incidence of Nd:YAG laser capsulotomy varies widely.[15] The higher levels in this study reflect an increased tendency to treat based on reduced contrast sensitivity rather than acuity or appearance. Cases of wrinkling of the posterior lens membrane (PLM) were also treated early since this caused a reduction in contrast sensitivity.

Implantation of both lenses was straight forward under normal conditions. However the flexibility of the polymacon lens proved a disadvantage in a shallow anterior chamber. Contact between the lens and any surgical instrument resulted in displacement due to the high coefficient of friction of the material compared with PMMA. Postoperatively its flexibility can allow the lens to bow forwards rather than backwards as the capsular bag contracts leading to iris damage and pigment liberation which can be seen on the lens. Previous studies have shown an increased tendency for pigment liberation associated with polymacon lenses.[7 9 10]

Although the groups are not large enough for statistical analysis of the complications the complete dislocation of three polymacon lenses is worrying. One lens dislocated 5 days after a YAG laser capsulotomy through a 4·5 mm gap. Similar occurrences have been reported.[4,5,9] The other two began to dislocate 6 months after an apparently routine operation and follow up. One appeared to be outside the bag inferiorly and eroding through the zonules, the other had already dislocated into the vitreous when seen. In both cases the posterior capsule itself appeared intact. This problem has not been reported previously. Dislocation due to capsule rupture and due to unspecified causes have been reported.[5,8] It has already been established that the haptics of this type of polymacon lens can escape from the capsular bag postoperatively.[9] In one series of polymacon lenses three were placed in the eye despite capsule rupture without any short or long term problems.[7] In another series a lens placed in an eye with a ruptured posterior capsule subsequently dislocated.[4] A lens dislocation following 'spontaneous' capsule rupture 4 months after operation has also been described.[9] Damage to the posterior capsule would, in the authors' opinion, preclude the use of a polymacon lens due to the risk of subsequent dislocation. Capsulotomies should also be kept as small as practicable. The manufacturers of this lens recommend a minimum period of 90 days after operation before performing a capsulotomy.

Another difference is in the number of 'fibrin' membranes associated with the polymacon lens. These occurred between 3 and 7 days after operation. The patient's eye appeared quiet with virtually no cells in the anterior chamber while the lens was coated by the membrane and posterior synechiae were evident. Although the membrane absorbed over a period of weeks the synechiae persisted. Three patients were distressed by a sudden decrease in vision. The authors have never encountered such reactions with PMMA lenses. The membrane associated with one PMMA lens in the trial was difficult to see, and was associated with typical signs of a mild anterior uveitis which did not affect the patient's acuity. Mild fibrin reactions with polymacon have been noted before.[4,9] In cats a monolayer of fibroblasts has been shown to coat the polymacon lens.[3]

Dislocation, though rare, makes these lenses impractical in their present form. It is also possible that movement could lead to a variation in refractive error. A flexible material has obvious advantages for small incision surgery. The hydrophilic surface may be more biocompatible with advantages for the corneal endothelium, healing and, indeed, if removal of the lens is necessary. Polymacon is also more resistant to YAG laser damage,[16] though we did not find any obvious advantages regarding posterior capsule opacification which had been suggested.[4]

In summary we have reservations about the modulation transfer function of polymacon in vivo and its association with 'fibrin' membranes. It may yet prove to be a useful material for the optic of a lens. However a material which becomes fixed in the eye would be more appropriate for the haptic since long term stability is essential for any intraocular lens.

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Improved iodine-125 plaque design in the treatment of choroidal malignant melanoma

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Abstract

The use and development of iodine-125 plaque therapy for choroidal malignant melanoma are described. Since 1975 experience has led to changes in plaque design and insertion techniques. Twenty-one patients were irradiated with local episcleral iodine-125 plaques. Three patients required a second plaque for tumour recurrence. Four eyes were enucleated because of continued tumour growth and a further eye was removed because of glaucoma secondary to radiation retinopathy. Two patients (9·5%) died of metastases. The remaining 19 patients are alive and clinically clear of metastases, with a mean follow up time of 73·1 months (range 43–142 months).

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Radiation therapy has become an established form of therapy for posterior uveal malignant melanomas.[1,2] Interest in this modality has increased since Zimmerman and co-workers[3-5] suggested that enucleation may be detrimental to the patient because of the sharp increase in the incidence of death from metastases which occurs after the operation. Though external radiotherapy in the form of proton beam irradiation[6] and helium ion therapy[7] are being used they are only available in a few centres. The application of local radiotherapy administered by radioactive episcleral plaques has gained widespread acceptance.

Radon seeds were introduced by Moore[8] in 1930. In 1966 Stallard reported the use of cobalt-60 plaques in a large number of patients with choroidal malignant melanomas,[9] and several other studies have since been published.[10-15] Because of the inherent problems encountered with this high energy source various attempts have been made to use low energy radioactive sources. Lommatzsch[16] used ruthenium-106 but did not recommend its use for tumours thicker than 5 mm. Rotman *et al*[17] mentioned the use of iodine-125 and in 1976 Sealy *et al*[18] first reported the use of this isotope in three patients with ocular tumours including one with a choroidal melanoma. Subsequently Stannard *et al*[19] reported the use of iodine-125 plaques in the treatment of retinoblastoma. The low energy rays of iodine-125 permit easy screening of nearby structures. The radiation is 99·9% absorbed by a sheet of gold 0·2 mm thick which compares favourably with cobalt-60 which requires an 11 mm block of lead to attenuate it by 50%.[18,20,21] The isotope emits *x*-rays with an energy of 27 to 35 keV, and has a relative biological effectiveness (RBE) of 1·5 relative to cobalt-60.[22] Moreover it has recently been reported that the oxygen enhancement ratio for iodine-125 is less than that of iridium-192 and the RBE is especially high for hypoxic cells.[23] For the purpose of plaque therapy the tissue penetration is good and similar to high energy isotopes over short distances.[24] The tissue half value layer is 20 mm which allows large choroidal melanomas to be treated.

Iodine-125 is supplied, absorbed onto silver rods or resin beads, in the form of seeds measuring 4·5 mm in length and 0·75 mm in diameter. The short half-life of iodine-125 (60 days compared with 5·26 years for cobalt-60) is a disadvantage but, as the seeds are commercially available and can be re-used several times during this period, this does not constitute a major

Table 1 Summary of patient data and treatment

Patient	*Age*	*Sex*	*Eye*	*Size (mm) (L×W×H)*	*Position*	*Proximity to optic nerve (mm)*	*Date of plaque*	*Follow up (months)*	*Initial VA*	*Final VA*	*Dose apex TDF (Gy)*	*Repeat plaque*	*Notes*
GO	58	F	R	15×15×7	ST	0	20/3/75	139	CF	E	170 (110)	N	Recurrence
QL	59	F	R	10×9×8	IT	7	19/4/78	142	6/12	E	90 (50)	N	RD, RR, glaucoma
MB	67	F	L	13×16×6	T	4	8/5/78	105	6/24	E	105 (50)	N	Recurrence
HL	59	M	L	11×12×5	IN	0	9/6/80	114	6/12	6/12	164 (112)	N	Cataract
JH	67	M	L	10×10×6	ST	5	9/10/81	43	6/9	6/24	144 (126)	Y	RD, recurrence, Mets
BG	72	F	L	12×15×4	SN	2	23/9/83	76	6/6	6/6	115 (61)	N	
MW	20	M	R	20×19×5	SN	1	3/2/84	74	6/24	E	174 (81·4)	Y	RD, recurrence
RG	44	M	L	10×10×8	IN	5	17/2/84	78	6/6	CF	164 (80)	N	RD, cataract
LA	42	F	R	6×8×5	T	3	12/3/84	72	6/12	CF	166 (80·6)	N	RR
KB	60	F	R	10×10×5	ST	2	19/4/84	71	6/9	6/18	165 (80)	N	
AA	45	M	L	12×10×6	IN	5	24/9/84	68	6/5	6/18	152 (44)	N	RD, RR, cataract
WG	73	M	L	11×11×8	IN	1·5	3/10/84	58	6/60	HM	153 (48·2)	N	RR
DM	62	F	L	8×8×4·9	IN	0	23/11/84	65	6/6	6/12	149 (47·7)	N	
MH	57	M	R	12×12×4·3	IT	2	14/1/85	64	CF	CF	158 (43·7)	N	
AH	47	F	R	6×6×4·6	T	5	11/2/85	53	6/9	6/24	150 (44·8)	N	RR
EP	25	M	R	12×9×7·6	IT	6	19/2/85	61	6/9	E	150 (45·4)	N	Recurrence
VJ	55	L	R	9×7·5×5·2	IT	1	25/6/85	60	6/12	CF	150 (45·4)	N	RR, Vit hx, cataract
DS	39	F	L	11×9×7·5	I	2	9/7/85	53	6/9	HM	145 (40·7)	N	RR, cataract
NG	58	M	R	16×15×10·2	T	6	11/2/86	47	6/12	CF	154 (66)	N	RR, Vit hx, Mets
LK	32	F	L	12×12×8·2	IN	0	8/8/86	46	CF	HM	152 (78·6)	N	RD, RR
MC	69	F	R	9×9×7·8	IT	2	30/9/86	46	6/24	6/9	99·5 (57·5)	Y	Recurrence

VA=visual acuity; CF=count fingers; HM=hand movements; E=enucleation, RD=pre-operative retinal detachment; RR=radiation retinopathy, Vit hx=vitreous haemorrhage, Mets=died of metastatic disease, ST=superotemporal; IF=inferotemporal, SN=superonasal, IN=inferonasal; S=superior, I=inferior

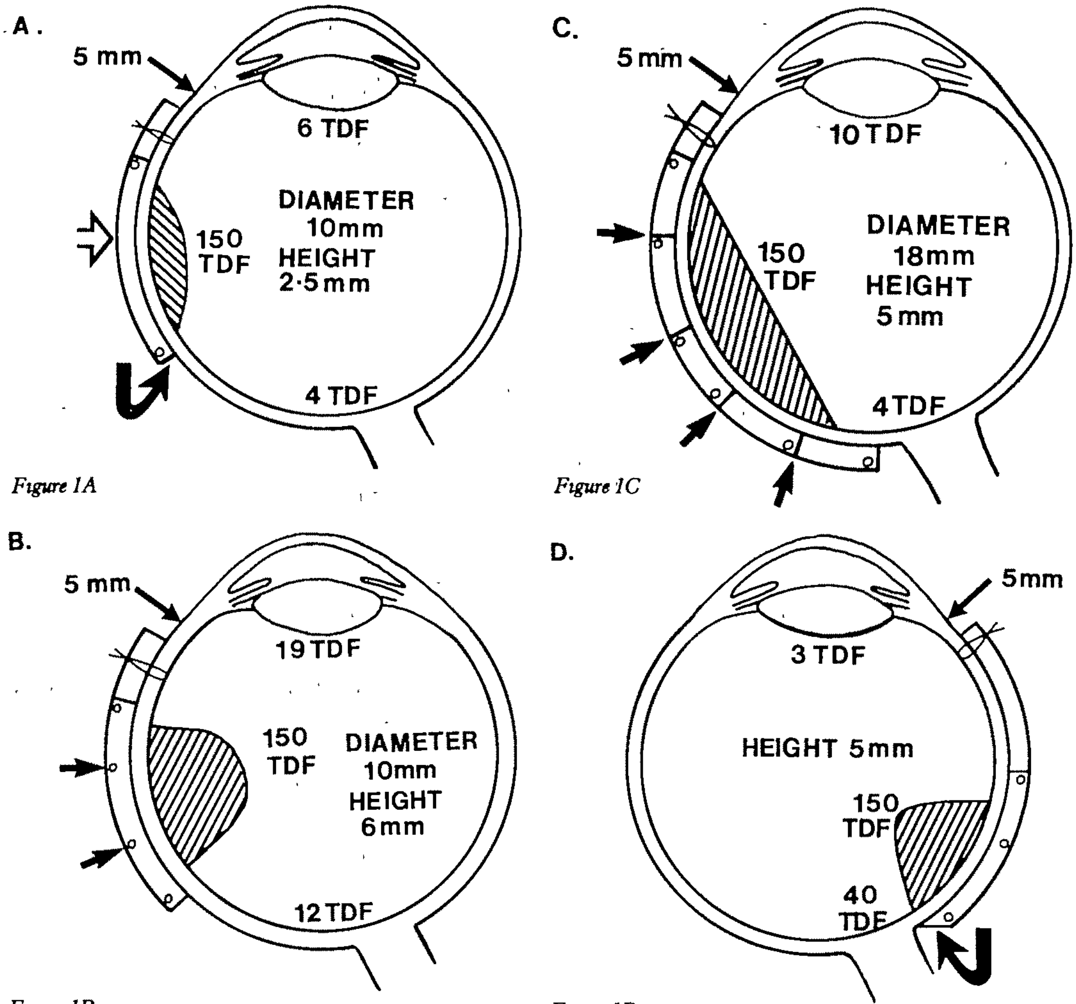


Figure 1A

Figure 1B

Figure 1C

Figure 1D

Figure 1 Diagrammatic representations of various plaque designs for tumours of different sizes and position. (A) Standard plaque. Small rather flat lesion. No shielding other than returned edge (arrow) and backing (open arrow) needed. (B) Extra sources (arrows) added to ensure an adequate dose to apex and to base of tumour. (C) For larger lesions with many sources, it is necessary to place sources against ridges (arrows) to protect adjacent structures. These extra sources are needed to ensure a homogeneous dose to the base. Note returned edge protects optic nerve. (D) The tumour reaches the optic nerve but does not invade it. The returned edge is angled outwards at 45° (arrow) to throw the beam wider at this point, the oblique beam passing over the optic nerve.

problem. The excellent screening characteristics, good tissue penetration, low oxygen enhancement ratio, and high RBE make iodine-125 an ideal source for local radiotherapy treatment of choroidal melanomas and other tumours in and around the eye. Recently iodine-125 was selected for use in the Collaborative Ocular Melanoma Study.[25] This paper presents our experience with this isotope for the treatment of choroidal malignant melanomas and discusses the change in plaque design since our earlier communications.[18 26]

Patients and methods

Twenty-one patients with choroidal malignant melanomas were treated with radioactive iodine-125 plaques during the period 1975 to 1986. Eleven females and 10 males are included in this series with a mean age of 52·6 years (range 20–73 years) (Table 1). All patients were jointly assessed in a combined ophthalmology-radiotherapy clinic. A full clinical examination was performed together with a full blood count, erythrocyte sedimentation rate (ESR), serum chemistry and liver enzymes, chest x-ray and, on most patients, a liver ultrasound examination. All the patients were free of metastases at the time of operation. Ophthalmic assessment included direct and indirect ophthalmoscopy (and fundus contact lens when indicated), fundus photography, fluorescein angiography, ultrasonography, and transillumination. The tumour dimensions were measured clinically and tumour height in later cases was obtained by B-scan ultrasonography. On occasions an examination under anaesthetic was performed especially with anterior tumours. This permitted accurate delineation of the anterior edge and in particular the posterior extent of the lesion could be judged when retinal detachment was present, by performing conjunctival peritomy followed by gentle posterior indentation and transillumination. Ultrasonography and computed tomography (CT) scans were used to help delineate the posterior edge when retinal detachment was present. Recently we have also used magnetic resonance imaging (MRI) scans.[27]

According to Shields's classification[1] seven tumours treated in this series were classified as medium sizes and 14 as large (Table 1). The

Table 2 Calculated radiation doses to optic disc and lens, showing the importance of returned plaque edges

Plaque dimensions			*Dose to optic disc*		*Dose to lens*	
Sagittal (mm)	*Coronal (mm)*	*Plaque position*	*Without edge (Gy) (TDF)**	*With edge (Gy) (TDF)*	*Without edge (Gy) (TDF)*	*With edge (Gy) (TDF)*
10	10	Centred on equator	10·2 (19)	6·2 (10)	13·0 (27)	8·3 (14)
10	25	Centred on equator	15 4 (33)	7·6 (13)	19·5 (46)	10 0 (19)
20	10	Abutting optic nerve	76 7 (292)	27 2 (72)	11·0 (21)	8·1 (14)
20	25	Abutting optic nerve	78·0 (299)	14·3 (30)	15·1 (32)	8·4 (15)

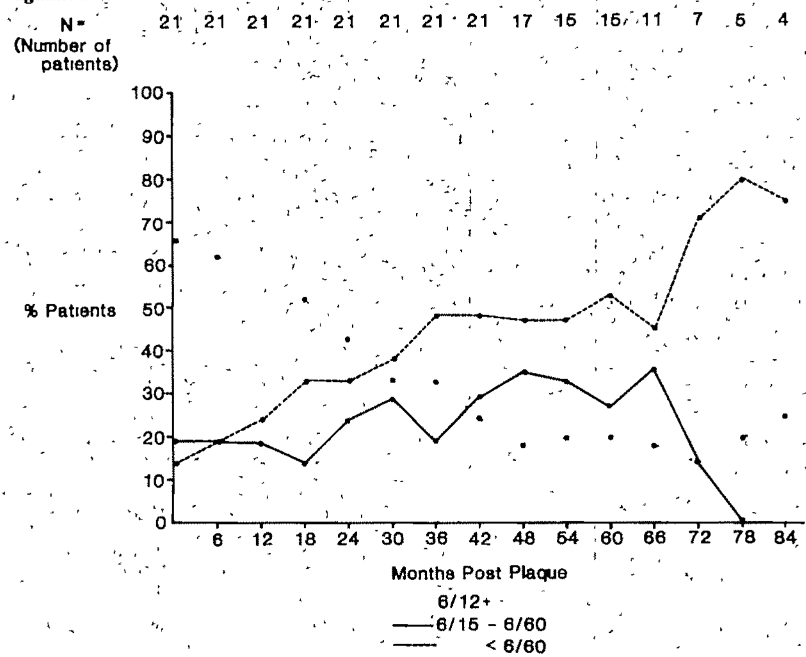
*Time-dose factor (TDF) values are shown in parentheses and assume an RBE of 1·5. Tumour height is taken as 5 mm, tumour apex TDF dose is 150, and treatment time is 4 days in each case mean dimensions of the tumours treated (length ×width×height) were 11·2×11·1×6·35 mm (range 6–20×6–19×4–10·2 mm).

Plaque design

All plaques are designed and made on an individual basis by the radiotherapist, the medical physicist, and technical staff. If optimum shielding is to be obtained 'standard' plaques cannot be used because of variations in tumour size and height and the variable relationship of tumour to the optic nerve, macula, lens, and ciliary body. The position of the tumour is drawn on a model eye with coordinates marked on it as described by Stannard *et al.*[19]

The manufacture of the gold backing and returned edge is similar to that described previously.[26] The returned edge prevents radiation being emitted sideways from the plaque. This reduces the dose to adjacent normal tissues provided the edges are straight and the seeds are placed adjacent to the edge (Fig 1). Ridges within the plaque control the distribution of the radiation (Fig 1C). Table 2 gives theoretical examples of radiation doses received by the lens and nerve head for various sizes of plaque in different positions, with and without the returned edge. The effective shielding of these structures allows lesions close to the optic nerve to be irradiated more safely. Large high tumours are difficult to treat by other types of plaque as effective radiation doses cannot be given to the apices of the tumours without excessive radiation to other ocular structures. With our system the physical practical limit of the radioactive surface area of the plaque is about 400 mm² (20×20 mm). The design of the radioactive element of the plaque is calculated by a physicist, the number of seeds used is adjusted to allow an adequate dose of irradiation to the apex of the tumour within an acceptable time of 3–5 days. A range of doses and dose rates have been used in this series and the dosimetry has now been standardised for different dose rates using the TDF (time-dose factor) concept.[28] The mean TDF was 146 (range 90–174) taking the RBE of iodine-125 to be 1·5. The mean duration of time the plaque remained in situ was 103·2 hours or 4·3 days (range 62–144 hours). Seed activity is usually about 4 mCi but seeds with 20 mCi activity can be used if an asymmetric dose distribution is required. The seeds are placed accurately in the plaque in their predetermined position and held in place with Tensol cement and, when dry, covered with a layer of thick acrylic solution. Loading time is about 1 hour.

Figure 2 Graphs to show percentage of eyes with vision in the three acuity groups against time.



The original plaques[18 26] were made to cover the tumour with a 3 mm margin. Scleral sutures were placed at the edges of the plaque; however insertion was technically difficult, especially with posterior lesions. This problem has been overcome by incorporating an anterior inactive extension to the plaque. The front edge of the plaque is then sutured to the sclera 5 mm posterior to the limbus, as depicted in Fig 1.

During insertion a sector limbal conjunctival peritomy is performed and the necessary external ocular muscles are detached. The radioactive plaque is introduced and sutured to the sclera, with the anterior edge 5 mm from the limbus, using the suture holes provided. There is thus no suturing or manipulation deep in the orbit except for transillumination or indentation along the edge of the plaque to check the relative positions of the plaque and tumour. The detached muscle(s) are temporarily attached to stainless steel loop(s) added to the outside of the plaque. There is excellent staff protection during the insertion of the plaque and the procedure takes approximately 30 minutes.

Results

The patients in this series were followed for a mean period of 73·1 months (range 43 to 142 months) (Table 1). Fifteen patients showed cessation of tumour growth. Five of these had almost complete tumour regression and in 10 the tumour decreased in size and especially in height. Six patients had recurrent or continued growth of their tumours. Three of these patients then underwent enucleation at 3, 54, and 60 months respectively after the plaque therapy. The other three patients received a second iodine-125 plaque: 4, 9, and 15 months respectively after the first application. One of these patients had the eye enucleated 13 months after the first plaque because of continued growth while the other two had cessation of growth. Two patients died of metastatic disease 43 and 46 months following plaque therapy: one was locally clear of disease and the other had had a successful retreatment with a second plaque. The remaining 19 patients are alive without evidence of metastases.

Four (28·6%) of the 14 patients who presented with useful vision of 6/12 or better retained useful vision. Four patients retained vision of 6/18 to 6/60. Three patients presented with visual acuities of less than 6/60 and a further 10 eyes lost vision to this level including patients undergoing enucleation. The overall trend was for patients to lose vision with time (Fig 2).

Complications are shown in Table 1. Five patients developed posterior subcapsular lens opacities following irradiation; four eyes have subsequently undergone successful lens extraction. Two eyes developed vitreous haemorrhage which was surgically cleared in one patient and has virtually resolved in the other. Nine patients showed evidence of radiation retinopathy with the occurrence of exudates and/or retinal haemorrhages. In three patients the exudative retinal detachment present before treatment extended soon after plaque therapy and resulted in further loss of vision. One eye developed neovascular glaucoma and was enucleated. No cases of optic atrophy, ocular hypotension, scleral necrosis, or dry eye occurred in this series.

Discussion

In this series two patients (9·5%) developed metastases and subsequently died. The other 19 are clinically free of metastatic disease. The mean follow up is 73·1 months. The number of patients treated in our study is small but the mortality rate is comparable to other studies: 5–12% with cobalt-60 plaques,[12,13,15] 17% with iodine-125 plaques.[29] All our patients had medium or large tumours with documented growth and would have been offered enucleation if radioactive plaques had not been available.

Though only four patients (19%) retained useful vision of 6/12 or better 16 patients (76%) retained their eye and thus avoided the psychological and cosmetic trauma of enucleation. With the passage of time the trend is for patients to lose vision following plaque therapy (Fig 2). Five patients in this study required enucleation, four for recurrent tumour growth. Two were among the earliest we treated with iodine-125 plaques: one patient's tumour was inaccurately localised because of a large serous retinal detachment and the other patient had recurrence at the tumour edge because of poor plaque placement. The new plaque design allows accurate placement of the plaque by aligning it to the limbus, and correct placement is confirmed by scleral indentation or transillumination along the side of the plaques. Another patient who had an enucleation for tumour recurrence was treated twice with iodine-125 plaque. His tumour was one of the largest tumours treated in the study measuring 20×19×5 mm; in addition a large retinal detachment was present on initial examination.

In this series there was a wide range of radiation doses and dose rates. Those patients receiving a higher TDF did not have an improved response. We now aim to deliver a TDF of approximately 150 to the apex of the tumour within 3–4 days provided that the doses to the optic nerve, ciliary body, and lens do not exceed the tolerance of these tissues.

The ability to screen the radiation from iodine-125 by gold foil ensures protection of staff and allows us to confine most of the radiation to the treated area thereby reducing the dose to surrounding sensitive structures, unlike cobalt-60 plaques where damage extends beyond this area.[30] It has also permitted us to treat tumours close to the optic disc with few complications. With cobalt-60 plaque therapy a 5 mm distance between plaque and optic disc is recommended.[31]

The tumours responding to irradiation demonstrated variable response. Five tumours showed good regression with marked diminution of tumour mass. The other 11 patients showed partial regression. Though reassuring to both patient and doctor total tumour regression is not necessary to ensure a good prognosis for either life or vision. Provided tumour growth can be curtailed the prospects of the patient retaining the eye and remaining free of metastases appear good.

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Periocular migration of hard contact lenses

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Abstract

Six cases are presented in which hard contact lenses have migrated into the periocular soft tissues, four into the eyelid, one into the orbit and one which spontaneously reappeared on the cornea 12 years after the patient had last worn contact lenses. Some possible mechanisms of this phenomenon and a review of the literature are presented.

The loss of a contact lens or displacement into the conjunctival fornices is a common occurrence. However erosion of a hard lens into the soft tissues around the eye is considered rare, only a few single cases are recorded. Six such cases of hard contact lenses embedding in the lids or orbit are described.

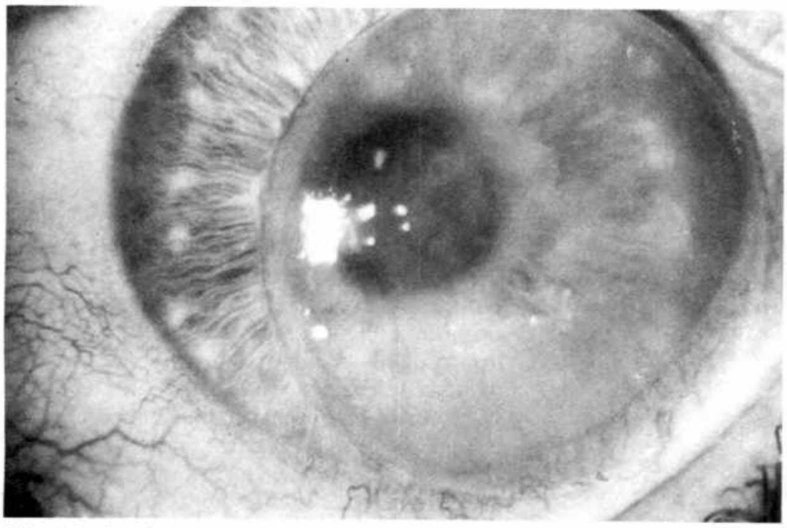

Figure 1 Case 1.

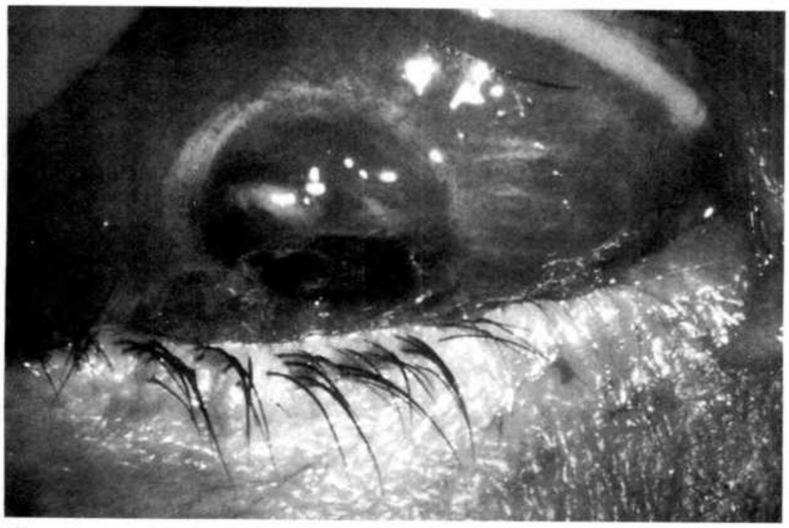

Figure 2 Case 3.

Case reports

CASE 1

A 70-year-old woman presented with a 2 hour history of painful sudden loss of vision in her right eye. Visual acuity was at the level of counting fingers at 2 metres. The eye was injected, photophobic, and watering. An encrusted hard contact lens was present on the cornea (Fig 1). Visual acuity improved to 6/12 and her symptoms resolved immediately once the lens was removed. In the past she had worn hard lenses and lost them on a number of occasions. She had last worn them 12 years before and in the interim had been symptom free. Eversion of the eyelid failed to reveal the site of emergence of the lens, but she was unable to tolerate double lid eversion. Electron microscopy of the lens showed it to be encased in a 200 μm thick layer of an amorphous deposit.

CASE 2

A 26-year-old woman presented with a slowly enlarging swelling, otherwise asymptomatic, of 6 months' duration in the left upper lid. She had lost a hard contact lens from her left eye some months before onset of the lid mass. A round, firm, non-tender swelling was evident medially within the tarsal plate. Lid eversion revealed an elevated disc of pale scar tissue on the subtarsal aspect of the lid. When the 'chalazion' was incised a hard lens was found under a thin layer of fibrous tissue. The lid returned to normal 2 weeks after removal of the lens.

CASE 3

A 56-year-old man attended complaining of a tender, swollen right upper lid for 3 days. On everting the lid a perfectly circular ring covered with conjunctiva was seen (Fig 2). A hard lens was removed following exploration of the lesion. The patient admitted having lost the lens 2 years earlier but in the meantime had been completely asymptomatic.

CASE 4

A 25-year-old woman gave a 3-month history of a slowly enlarging painless lump at the medial aspect of her left upper lid. A firm, smooth, non-tender mass was palpable above the tarsal plate in the anterior orbit. Fine needle aspiration biopsy was attempted and it then became apparent that the lesion was hard. Exploration revealed an encysted hard contact lens deep to the orbital septum. Both cyst and lens were removed with resolution of symptoms in 3 weeks. Histologically the cyst wall consisted of chronically inflamed conjunctiva.

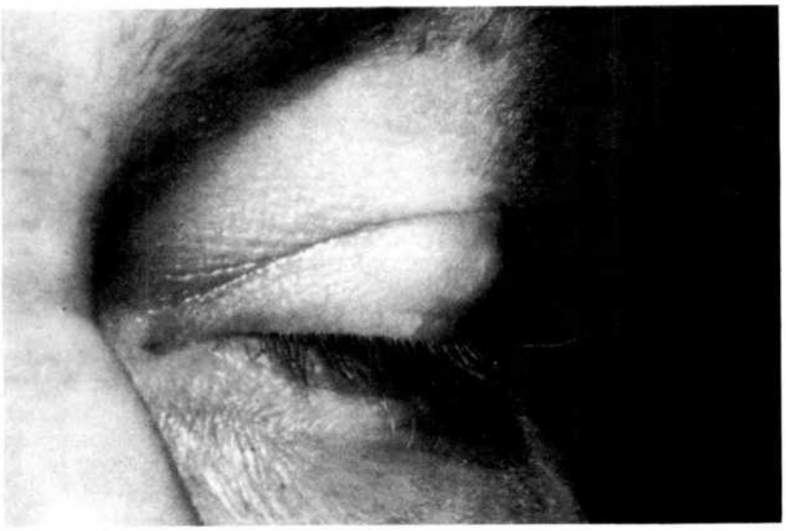

Figure 3 *Case 5.*

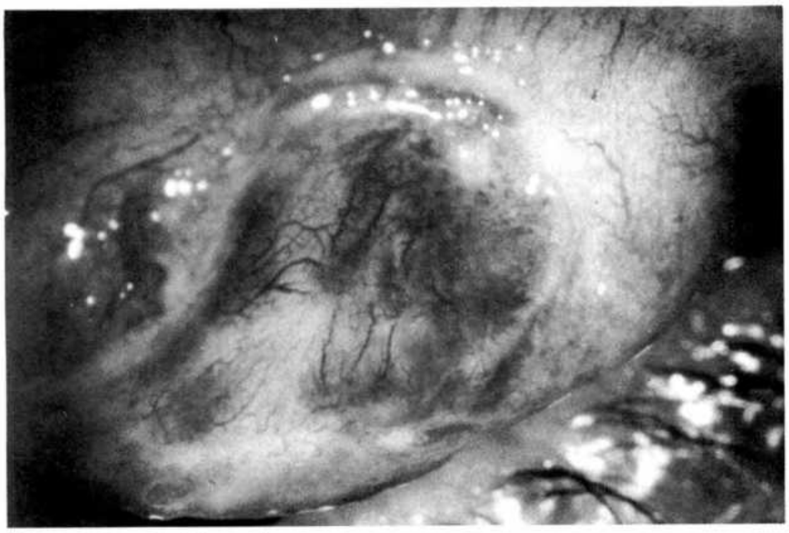

Figure 4 *Case 5 – lid everted.*

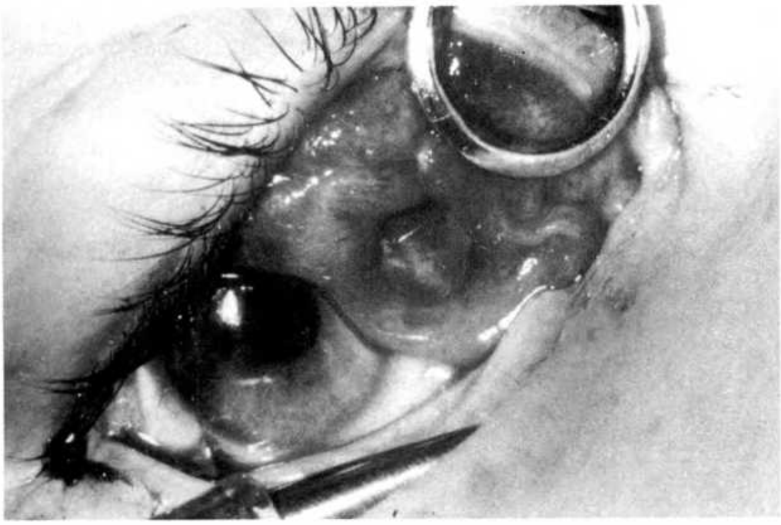

Figure 5 *Case 6.*

CASE 5

A young man noted a painless swelling in his left upper lid of several weeks' duration (Fig 3). An elevated, vascularised mass involving the tarsal plate was visible on lid eversion (Fig 4). Because of the rapid rate of onset and the aggressive appearance of the lesion, a meibomian gland carcinoma was suspected. At surgery a hard lens was found beneath the subtarsal conjunctiva. Removal of the lens was followed by full recovery within a few weeks.

CASE 6

A 19-year-old woman presented with an inflamed swelling medially in the right upper lid. A hard lens was discovered partly embedded in the subtarsal surface of the lid, with an elevated ring of hypertrophic conjunctiva around its circumference (Fig 5). She made a full recovery within 3 weeks of the lens being removed.

Discussion

The loss of a lens is a common problem among contact lens wearers. Usually the lens falls from the eye. Rarely, hard lenses may become embedded in the soft tissues around the eye. One possible explanation for this is that if the lens is displaced into the upper fornix the rim may engage the upper border of the tarsal plate and become trapped – the 'upper fornix trap'.[1] The action of the lid combined with pressure necrosis may lead to erosion of the lens into the adjacent tissues. A second theory suggests that the action of the upper lid on the displaced lens induces local abscess formation in the palpebral conjunctiva. Rupture of the abscess allows a point of entry for the edge of the lens to erode into the lid.[2] The absence of symptoms of irritation or discharge in some individuals challenges this idea. Erosion into the lid may occur without preceding abscess formation.[3]

Case 1 is unusual for the sudden reappearance of the lens after 12 symptom-free years. All other reported 'lost lenses' have produced symptoms or signs, for example localised lid swelling with or without tenderness,[2-9] discharge[4-6] or ptosis.[10 11] There is only one report of a lens reappearing, but, it was preceded by a 1-week history of lid swelling and the lens had been lost 1 month earlier.[6] Our case had been completely silent – she had even been examined ophthalmologically on a regular basis because of epiretinal membrane formation. Presumably pressure necrosis was responsible for release of the contact lens onto the cornea.

Case 4 is the second reported case of a hard lens being found in the orbit.[12] The surrounding cyst indicates that conjunctiva had been implanted into the orbit by the advancing edge of the lens. Epithelial lined cysts have also been noted surrounding contact lenses in the lids.[3 7]

The appearance of the lid lesion in case 6 is typical of a hard lens buried in the lid – an elevated ring of tissue surrounding a central crater.[4 5 9 12]

Including those featured here, 21 hard lenses have been reported embedded in the upper lid, two in the orbit and two that extruded from the lid. The majority of patients were young and female reflecting the prevalence of contact lens wear. Lenses in the lids have been confined without exception to the upper lid, with the majority in the medial aspect of the upper lid. The position of the lens within the lid also varies subcutaneously,[8] within the tarsal plate,[6] and under the tarsal or superior forniceal conjunctiva.[4 5 7 9-12]

X rays have been used in an effort to diagnose these unusual unidentified lesions, but it is not surprising that lenses cannot be detected radiologically.[2 5 7 10] Because of the big acoustic impedance mismatch between biological tissue and polymethylmethacrylate, hard lenses should be detectable on ultrasonography.[12]

It has been suggested that patients with hard lenses buried in their lids fall into two groups,[3] one in which there is a long time lapse (56 months or more) between loss of a lens and its retrieval, who have no mucopurulent discharge, and a second group of shorter duration that develop conjunctivitis. We feel that the difference in time span may merely reflect that patients who are in discomfort may present earlier than those with a silent lid swelling.

Several of our colleagues have commented on cases of lost contact lenses that have not been reported in the literature. This raises the suggestion that embedding of hard contact lenses in the periocular tissues is not in fact rare, merely uncommon, regarded as a novelty and left unreported.

Conclusion

Migration of hard contact lenses into the periocular soft tissues is a seemingly rare occurrence. Six cases are described, four of lenses embedded in the upper lids, one in the orbit and one extruding onto the cornea after being lost for 12 years. Lenses erode into the lid due to dynamic action of the lid, with or without local abscess formation. We suspect that this phenomenon is not particularly unusual but remains largely unreported and should be considered in the differential diagnosis of lid lesions in contact lens wearers.

We thank Mr J R O Collin and Mr R Downes for allowing us to report case 5 and Mr J Dart for the photograph of case 6

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Occurrence of pseudoexfoliation following penetrating keratoplasty for keratoconus

M Küchle, G O H Naumann

Abstract

The occurrence of pseudoexfoliation (PSX) following penetrating keratoplasty for keratoconus is reported in three eyes of two patients. The patients' ages at keratoplasty were 37, 40, and 31 years, and PSX was first observed 5, 4, and 6 years following keratoplasty. The donor age was 76, 81, and 81 years. Possible explanations for the occurrence of PSX after keratoplasty include mere coincidence, some sort of non-specific reaction to surgery or to postoperative medication, an immunogenic reaction to transplanted foreign corneal tissue, and the hypothetical speculation that PSX might be a transmissible disease.

Pseudoexfoliation (PSX) syndrome is clinically characterised by typical morphological changes of the anterior ocular segment. Despite numerous investigations its exact aetiology is still unknown.

We report three eyes of two relatively young patients with keratoconus in which PSX developed 4 to 6 years after corneal transplantation from donors over 75 years old.

Case reports

CASE 1

A 37-year-old white female was referred for treatment of bilateral keratoconus in 1981. Her family history and general history were uncontributory. Ocular examination of both eyes did not reveal any abnormality, except for bilateral keratoconus, especially no signs of PSX. Both eyes underwent 7·8/7·5 mm penetrating keratoplasty (right eye on 29 October 1981, left eye on 4 October 1984). The donors were a 76-year-old male and an 81-year-old male, respectively who had both died of myocardial infarction. The donor eyes were not specifically screened for PSX and were not available for histological examination. Postoperative medications were local corticosteroids (prednisolone acetate 1%) for 1 year and scopolamine eyedrops for 6 weeks. The postoperative courses were unremarkable in both eyes, and corrected visual acuity was 6/6 right and 6/7 left after suture removal. Both eyes underwent regular slit-lamp examination every 3 to 6 months by one of us (GOHN). In November 1986, 5 years after keratoplasty, the right eye showed signs of PSX for the first time (Fig 1). In November 1988, 4 years after keratoplasty, the left eye had also developed signs of PSX after having been normal 5 months earlier. On last examination in October 1990 both eyes showed abundant PSX material at the pupillary margin and on the anterior lens capsule, but neither eye developed increased intraocular pressure or any signs of glaucomatous damage.

CASE 2

In 1989 a 46-year-old white male was referred for penetrating repeat keratoplasty of the right eye and keratoplasty for keratoconus of the left eye. The patient's son had bilateral keratoconus. In 1974 the patient had undergone a penetrating keratoplasty for keratoconus of the right eye elsewhere. The donor had been an 81-year-old female. The donor eye was not available for histological examination. Postoperative medication had consisted of local corticosteroids. During follow up, development of PSX of the

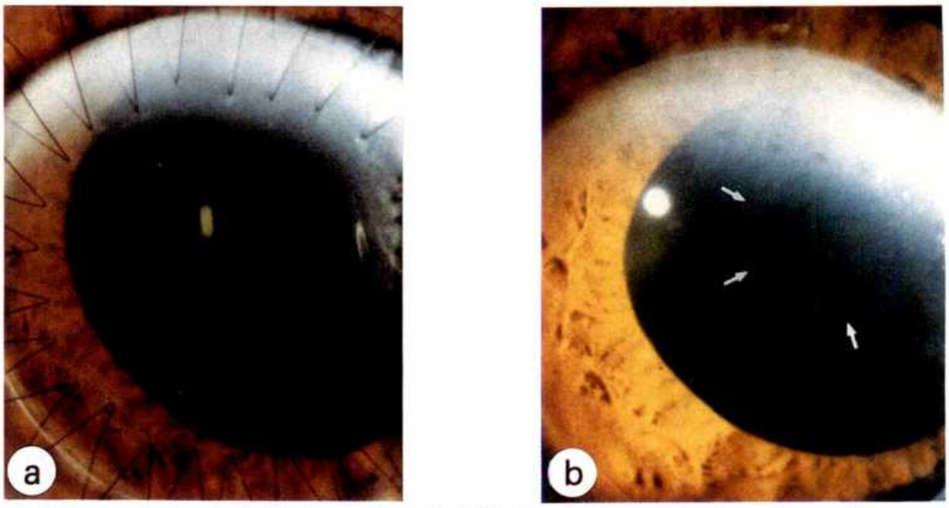

Figure 1 Right eye of patient 1. (A) Right eye in September 1984, 3 years after penetrating keratoplasty, without any signs of pseudoexfoliation. (B) Right eye in November 1986 displaying pseudoexfoliation material on the anterior lens capsule (arrows).

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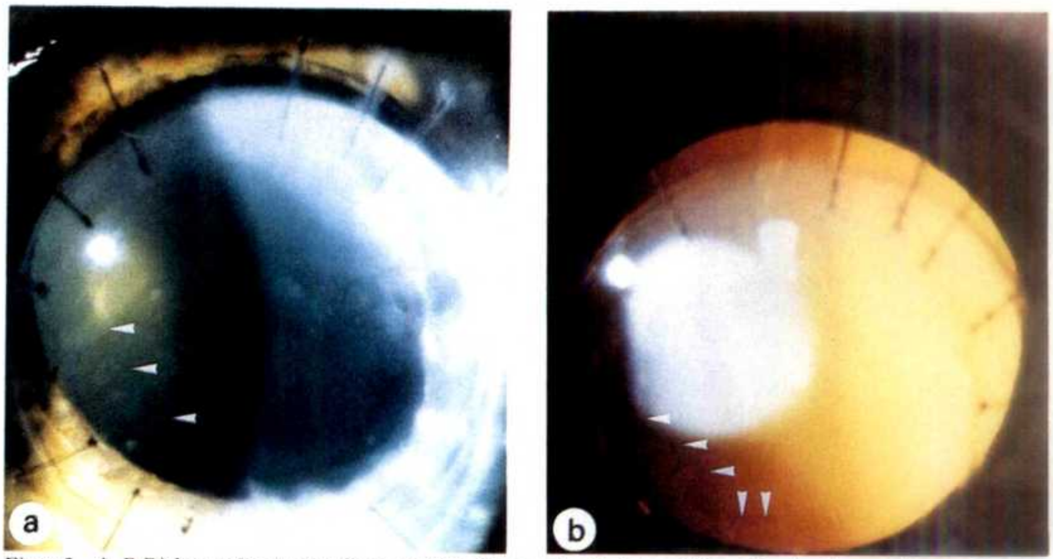

Figure 2 A, B Right eye of patient 2 in January 1991, 17 years after the first and 18 months after the second penetrating keratoplasty, with typical pseudoexfoliation material on the anterior lens capsule (arrowheads).

right eye was observed for the first time in 1980 – 6 years after keratoplasty. The right eye had also developed a corneal graft rejection. On slit-lamp examination the right eye showed abundant PSX material at the pupillary margin and on the anterior lens capsule. The left eye was completely normal except for keratoconus. Both eyes underwent 7·5/7·8 mm penetrating keratoplasty (right eye on 18 October 1989, left eye on 3 June 1990). The postoperative course was unremarkable in both eyes. On last examination in January 1991 corrected visual acuity was 6/7 in both eyes. The right eye showed the typical picture of PSX (Fig 2) whereas in the left eye there were no signs of PSX. Neither eye developed increased intraocular pressure or glaucomatous changes.

Discussion

PSX is of considerable epidemiological and socioeconomical importance because of its high prevalence in the aged population, its frequent association with open-angle glaucoma, and the increased rate of complications in PSX eyes during cataract surgery.[1]

Although the clinical picture, histological appearance, and ultrastructural characteristics of PSX have been thoroughly investigated in numerous studies the exact composition of PSX material as well as its aetiology are still obscure.

Recent ultrastructural studies[2-4] have demonstrated PSX material in various extraocular locations thus indicating that PSX is not confined to intraocular structures but may represent a more widespread disease.

Several authors[5-10] observed familial occurrence of PSX and assumed an autosomal dominant mode of transmission with incomplete penetrance. Other investigators[11,12] stressed the importance of environmental factors in the development of PSX. Klouman[13] and Ringvold *et al*[14] conducted population based studies on PSX. Both authors found an unexpectedly high incidence of PSX in both partners of married couples, a finding which was supposed to indicate an environmental influence on the distribution of PSX.

Our observation of the development of PSX after penetrating keratoplasty could be interpreted in several ways. (1) The occurrence could be purely coincidental. However our patients' ages at the development of PSX (42, 44, and 37 years) was exceptionally young. PSX is usually seen in older patients and only occasionally occurs in patients under age 50 although the youngest patient with PSX reported in the literature was only 31 years.[10] In our patients there was also a striking constancy of the interval between keratoplasty and development of PSX which was 4 to 6 years. (2) The development of PSX could represent a non-specific reaction to intraocular surgery or to local medication thus leading to the manifestation of PSX several years after keratoplasty. (3) The development of PSX could be the result of an immunogenic interaction between the host and the transplanted donor corneal tissue. The rather constant interval between keratoplasty and development of PSX could fit in with this hypothesis. (4) PSX could be a somewhat transmissible disease that in our patients was transmitted from the donors to the recipients by means of the corneal buttons. Unfortunately we do not know whether the donor eyes showed signs of PSX but as the donors were between 76 and 81 years of age and the prevalence of PSX is high in this age group it is possible that the donor eyes were affected by PSX. This speculation would again go well with the typical interval between keratoplasty and development of PSX in our patients and would also give some sort of explanation of the frequent occurrence of PSX in married couples seen by other investigators.[13,14]

Although the exact meaning of our observations is uncertain at present similar findings by other investigators may give important clues of the aetiology and pathogenesis of PSX in the future.

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Phenotypes of conjunctival inflammatory cells in sarcoidosis

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Abstract

Phenotypes of the infiltrating mononuclear cells of the lower fornix conjunctiva of nine patients with sarcoidosis and six controls were studied using monoclonal antibodies and a modified immunoperoxidase method. Four patients had sarcoidosis of recent onset (duration of 2 years or less) and five patients had a chronic disease (duration of 3 or more years). The inflammatory cells in the sarcoid conjunctival specimens were predominantly T lymphocytes, the vast majority of which were of T helper/inducer subtype expressing Leu-3a+3b positivity. The ratio of T helper/inducer cells to T suppressor/cytotoxic cells was 3·9 on average but only 0·9 in controls. Epithelioid cell granulomas were seen in three specimens in one case of recent onset and in two chronic cases comprising a marked amount (more than 15 cells/visual field) of cells bearing phenotypes of macrophages, T cells, T helper/inducer cells and HLA-DR antigen, and in smaller quantities of T suppressor/cytotoxic cells. The mean number of all immunocompetent cell subtypes of specimens from newly diagnosed patients exceeded that of specimens from chronic patients. We believe that the sarcoid immune reaction in the conjunctiva is a dynamic process in which proliferation of immunocompetent mononuclear cells precedes the stage of granuloma formation.

Sarcoidosis is a lymphoproliferative disease of unknown aetiology characterised by widespread epithelioid cell granulomas in more than one system. Bilateral hilar lymphadenopathy and/or pulmonary infiltration are seen in nearly every patient but any organ or tissue can be affected.[1] In three large clinical series consisting altogether of 1623 patients with sarcoidosis the frequency of ophthalmic manifestations varied between 25 and 38%.[2-4]

Patients with active sarcoidosis often show enhanced humoral immune activity with hyperreactivity of B-cells, raised immunoglobulin levels, and circulating immune complexes.[5] However sarcoidosis is above all a disease of increased immunological activity at specific disease sites leading to lymphocyte infiltration, monocyte recruitment, and granuloma formation.[6] By monoclonal antibody techniques it has become possible to differentiate the phenotypes of the immunocompetent cell subpopulations in sarcoid tissues. These studies concerning mainly pulmonary[6,7] but also extrapulmonary[8-12] sarcoid involvements revealed the central role of the T helper cells in initiating and modulating the granulomatous inflammatory response and the close interplay between the T helper cells and activated macrophages.[6,13]

There are only a few studies concerning the utilisation of monoclonal antibodies in detecting the immunocompetent cells in conjunctival sarcoidosis.[8,14] However the conjunctiva is an integral and active participant in the immunological defence system of the eye[15,16] and it is easily accessible for this kind of a study. By conventional histological examination Karma[2] found epithelioid cell granulomas in 17% of all 218 conjunctival biopsies and 33% of the chronic cases in her unselected sarcoid population. Furthermore Kargioğlu and Brear[17] identified granulomas in 71% of the sarcoid cases by random bilateral biopsy techniques. The purpose of this study was to examine with monoclonal antibodies the infiltrating cell profile in the conjunctiva of patients with recent onset and chronic sarcoidosis.

Patients and methods

Nine sarcoid patients (seven females and two males) aged 27 to 67 mean 52 (SD 13) years and six control patients aged 18 to 73 mean 46 (SD 22) years were studied. The clinical features of the sarcoid patients are shown in Table 1. Four patients (cases 1 to 4) had sarcoidosis of recent onset (duration 2 years or less) and five patients (cases 5 to 9) had chronic disease (duration 3 years or more). All individuals also had extrathoracic sarcoid manifestations in addition to pulmonary changes. In six patients sarcoidosis has been verified histologically. Four patients had uveitis two of whom additionally had retinal vasculitis (cases 6 and 7) and one patient also had an optic disc granulomatosis (case 7). One patient (case 2) without uveitis had a choroidal granuloma of suspected sarcoid origin. Patient 1 presented with a huge iris node. All subjects were assessed as having an active sarcoidosis based on clinical symptoms and/or elevated serum angiotensin converting enzyme (SACE). The chronic patients had higher mean SACE value (195 (SD 72) units/l) than the newly diagnosed individuals (81 (SD 27) units /l, p=0·021). Four patients (cases 1, 6, 7, and 9) were receiving systemic prednisolone therapy and two additional individuals (cases 1 and 5) were receiving topical dexamethasone at the time of the conjunctival biopsy.

In two patients (cases 6 and 8) the conjunctiva of the lower fornix looked quiet on slit-lamp examination, but in seven patients follicles in the lower fornix were seen and assessed as typical of sarcoidosis (Fig 1) in four patients (cases 4, 5, 7 and 9). We either biopsied one of the follicles or took a piece measuring 2×2×3 mm on average of the normal looking lower fornix conjunctiva. Forniceal conjunctival tissue was also obtained from six non-sarcoid patients undergoing

Table 1 Clinical findings in nine patients with sarcoidosis

Case no.	Age (years) sex	Duration of disease (years)	Site of histological verification	Abnormal chest x rays	Other sarcoid manifestations	SACE (units/l)*	Systemic prednisolone
						at the time of the conjunctival biopsy	
1	27,M	<1	Bronchial mucosa	Yes	Nodular iritis, joint symptoms	60	Yes
2	67,F	<1	Mediastinal lymph node	Yes	Choroidal granuloma	114	No
3	41,M	1	–	Yes	Neurological symptoms	57	No
4	49,F	2	–	Yes	Erythema nodosum	93	No
5	57,F	3	Lung	Yes	Uveitis, lacrimal gland affection, peripheral neuropathy	106	No
6	56,F	7	–	Yes	Uveitis, retinal vasculitis	212	Yes
7	44,F	10	Bronchial mucosa, lacrimal gland, skin, gallbladder	Yes	Uveitis, lacrimal gland affection, optic disc and choroidal granulomas, retinal vasculitis, hypophysis-hypothalamus lesion in CT, lupus pernio, cholecystopathia	135	Yes
8	66,F	11	Lung	Yes	Peripheral lymphadenopathy, parotid affection, erythema nodosum	270	No
9	58,F	16	Mediastinal and peripheral lymph nodes, skin	Yes	Lacrimal gland affection, peripheral lymphadenopathy, lupus pernio	254	Yes

*Serum angiotensin-converting enzyme, range of normal values 35–155 units/l.

cataract (four), strabismus operation (one), or enucleation for choroidal melanoma (one). None of the control patients showed signs of non-specific conjunctival inflammation but in one patient a few follicles were seen. Consent for the biopsy procedure was obtained from each subject.

The biopsy specimens were snap frozen and 6 μm thick serial sections were prepared. A modified avidin-biotin-peroxidase technique[18] was utilised (Zymed laboratories). Dilution of the primary monoclonal antibodies (Becton Dickinson Monoclonal Center) and their specificities are shown in Table 2. The secondary antibody was biotinylated horse anti-mouse IgG. Human lymph node served as a positive control. Two sections of each cell surface marker (primary antibodies) were prepared. One section was counterstained with Harris haematoxylin and the other was left unstained.

Figure 1 Yellowish nodes typical of sarcoidosis in the lower fornix conjunctiva (arrows).

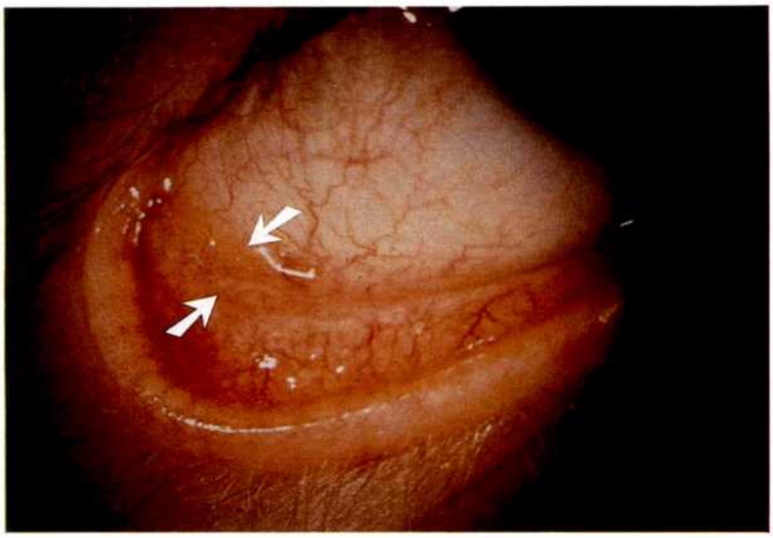

Table 2 Characterisation of monoclonal antibodies

Antibody	Antigen cluster designation	Dilution of antibody	Predominant reactivity
Anti-Leu-4+5b	CD3, CD2	1:15	T cells
Anti-Leu-3a+3b	CD4	1:2	T helper/inducer cells
Anti-Leu-2a	CD8	1:30	T suppressor/cytotoxic cells
Anti-Leu-14	CD22	1:4	B cells
Anti-Leu-7	–	1:20	NK (natural killer) cells
Anti-Leu-M5	–	1:40	Monocytes, macrophages
Anti-HLA-DR	–	1:60	B cells, monocytes macrophages, activated T cells

We scanned through all the specimens and depending on the size data were collected from 10 to 90 different consecutive ×40 high power visual fields. The average number of positive cells/visual field for each primary antibody was obtained by dividing the total number of positively stained cells by the total number of visual fields counted. In addition the areas of granulomas and follicles were evaluated separately. The total number of positively stained cells in the area of granuloma/follicle was divided by the number of visual fields covering the granulomatous/follicular structure. The number of positively stained cells/visual fields was semi-quantitatively determined in the area of the granuloma/follicle with the positivity being graded as follows: negative zero cells; mild from one to six cells; moderate from seven to 15 cells; and marked more than 15 cells. Statistical analyses were performed using the one-way analysis of variance.

Results

The phenotypic profile of the infiltrating mononuclear cells in the conjunctival specimens and that in the granulomatous/follicular areas of the sarcoid patients are shown in Tables 3 and 4. The inflammatory cells in the sarcoid conjunctival specimens were predominantly T lymphocytes identified by staining with anti Leu-4+5b antibody. The vast majority of the T cells were, in all specimens except one (case 6), of T helper/inducer subtype expressing Leu-3a+3b

Table 3 Phenotypic profile of the inflammatory cells in the conjunctiva of the sarcoid patients

				Leu-3a+b				
Case No	*Leu-4+5b*	*Leu-3a+3b*	*Leu-2a*	*Leu-2a*	*Leu-14*	*Leu-7*	*Leu-M5*	*HLA-DR*
1	15·8	15·3	2·8	5·5	15·7	1·4	1·0	16·6
2	23·0	77·9	25·9	3·0	15·2	0·7	7·7	22·2
3	65·1	40·4	6·6	6·1	80·6	1·5	9·7	80·0
4	25·4*	56·6	17·0	3·3	19·3	0	24·4	140·8
5	42·9	40·8	3·1	13·2	6·2	0·2	5·9	11·8
6	8·3	3·8	2·5	1·5	0	0	0·1	2·7
7	20·1*	15·1*	4·1*	3·9	1·4	0	12·7	26·6*
8	7·8	8·7	1·9	4·6	1·1	ND	2·4	5·5
9	20·6*	15·6*	3·7*	4·2	0·5	ND	4·2	3·7*
Mean (SD) no of positively stained cells in								
All	25·4 (16·9)	30·5 (18·0)	7·5 (6·4)	3·9	15·6 (19·7)	0·5 (0·5)	7·6 (6·9)	34·4 (36·3)
Cases 1–4	32·3 (22·2)	47·6 (24·4)	13·1 (10·4)	3·7	32·7 (32·0)	0·9 (0·7)	10·7 (9·9)	64·9 (58·2)
Cases 5–9	19·9 (26·5)	16·8 (14·3)	3·1 (0·9)	5·7	1·8 (2·3)	0·1 (0·1)	5·1 (4·8)	10·1 (9·9)
Ratio (cases 1–4/ cases 5–9)	1·6	2·8	4·2	0·6	18·2	9·0	2·1	6·4
p value†	0·269	0·067	0·039	0·994	0·002	0·099	0·391	0·024

* Indicates specimen in which epithelioid cells were identified.
† Using one-way analysis of variance after logarithmic transformation of data
ND=no data

positivity. The mean number of T helper/inducer cells outnumbered the T suppressor/cytotoxic (Leu-2a positive) cells by 3·9 times on average being 3·7 in the newly onset patients and 5·7 in the chronic patients. In only one specimen (case 3) did the mean number of the B cells (Leu-14 positive) outnumber the T cells. On the other hand in four of the five chronic cases B cells were nearly or totally non-existent.

The positively stained cells in the conjunctival specimens were mainly located subepithelially (Figs 2 and 3) and scattered less frequently in substantia propria (Fig 3). A few scattered lymphoctyes and HLA-DR positive cells were also seen intraepithelially (Fig 3). Among diffuse infiltrations aggregates of diverse cell subtypes arranged more or less follicularly could be seen in nearly every section (Figs 4–7 and Table 4).

True granulomas (Figs 5–7) were observed in only three specimens, in one newly-onset case (no 4), and in two chronic cases (nos 7 and 9) (Tables 3 and 4). However epithelioid cells could not be identified in all sections in these specimens (Fig 5). The granulomas were composed predominantly of cells bearing monocyte (Leu-M5, Fig 5), T cell (Leu-4+5b, Figs 6 and 7), and T helper/inducer cell (Leu-3a+b) phenotypes. In two cases a moderate number of T suppressor/cytotoxic cells were identified in the granulomas (cases 4 and 7, Table 4), but in one case (no 9) only a very few suppressor cells were detected. In two specimens the suppressor T cells were seen in the periphery of the granulomas but in the third they were seen in the middle of the granulomas as well. All sarcoid granulomas showed a marked positivity with anti HLA-DR antibodies.

There was a large difference in the number of all immunocompetent cells and their subtypes between the newly diagnosed and chronic cases (Table 3). The mean total numbers of T lymphocytes, T helper/inducer cells, T suppressor/cytotoxic cells, and macrophages in the patients with newly onset sarcoidosis were 1·6–4·2 times greater than the corresponding number of the cells in chronic sarcoidosis. The difference was statistically significant for T suppressor cells (p=0·067).

Furthermore the mean total number of HLA-DR positive cells and Leu-14 positive cells (B lymphocytes) in the newly onset cases exceeded the corresponding number of the chronic cases by 6·4 (p=0·024) and 18·2 (p=0·002) times respectively.

In one control specimen taken from an evident follicle a marked positivity (>15 cells/visual field) of T lymphocytes and their subtypes was seen and in another specimen from a melanoma patient the HLA-DR positivity was marked. In the rest of the control specimens the number of immunocompetent cells was scanty. The ratio of T helper/inducer cells to T suppressor/cytotoxic cells of the control specimens ranged between 0·5 and 1·7, the mean ratio being 0·9.

Discussion

Sacks and coworkers[19] studied, using monoclonal

Table 4 Phenotypic profile of the inflammatory cells in the conjunctival lymphoid follicles and granulomas

Case	*Leu-4+5b*	*Leu-3a+3b*	*Leu-2a*	*Leu-14*	*Leu-7*	*Leu-M5*	*HLA-DR*
1	++	++	+	+++	+	0	++
2	++	+	+	++	0	++	++
3	+++	+++	++	+++	+	+	+++
4	+++*	+++	++	+++	0	+++	+++
5	0	+	+	++	0	++	+
6	++	++	+	0	0	0	++
7	++*	+++*	++*	+	0	+++	+++*
8	++	+++	+	+	ND	+	++
9	+++*	++*	+*	0	ND	+++	+++*

Grading of positivity (mean number of positively stained cells/visual field) 0 (negative, zero cells), +(mild, from one to six cells), ++ (moderate, from seven to 15 cells), +++(marked, more than 15 cells)
* Indicates specimen in which epithelioid cells were identified
ND=no data

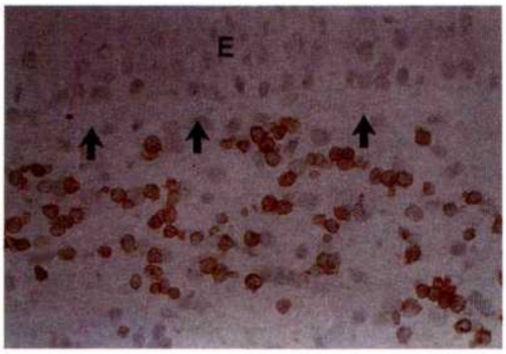

Figure 2 Case 6. Inflammatory subepithelial cells in the conjunctiva stained with anti T cell antibody (Leu-4+5b). E indicates epithelium and arrows indicate demarcation between epithelium and substantia propria. Counterstained with Harris haematoxylin (×310).

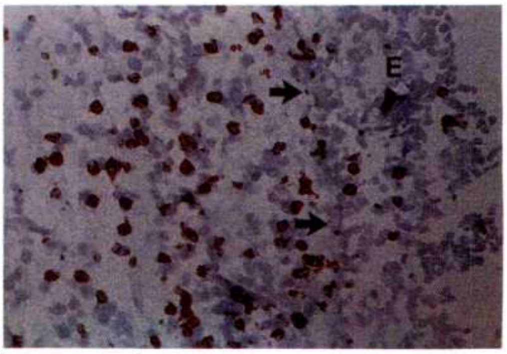

Figure 3 Case 2. Diffuse infiltration of T cells (Leu-4+5b positive) subepithelially and in the substantia propria. A few positive cells are seen also intraepithelially. E indicates epithelium and arrows indicate demarcation between epithelium and substantia propria. Counterstained with Harris haematoxylin (×260).

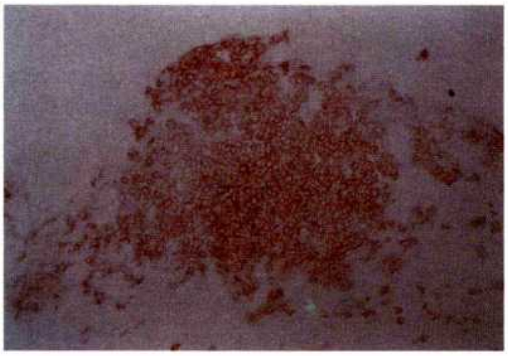

Figure 4 Case 8. Aggregates of T helper/inducer cells (Leu-3a+3b positive) in the connective tissue of substantia propria (×100).

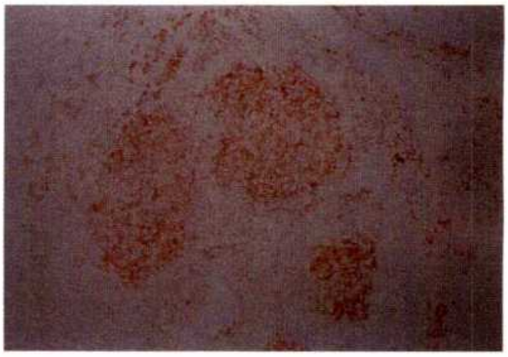

Figure 5 Case 7. Sarcoid granulomas in substantia propria showing marked positivity with antimacrophage antibody (Leu M5) (×100).

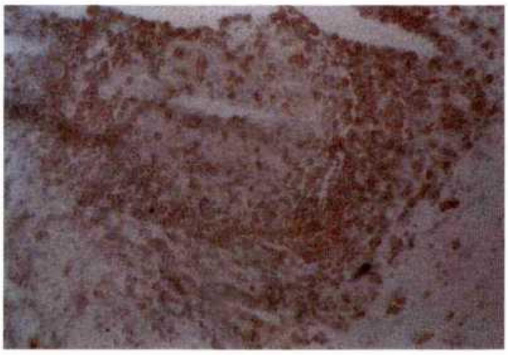

Figure 6 Case 4. Sarcoid granuloma in substantia propria showing marked positivity with anti T cell antibody (Leu-4+5b). A vast majority of T cells were of T helper/inducer subtype. Counterstained with Harris haematoxylin (×100).

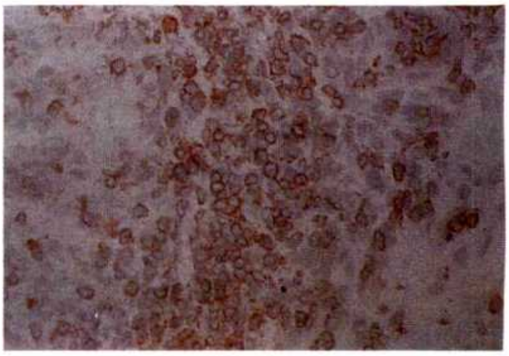

Figure 7 Case 4. Enlargement of Fig 6. There were many fewer T cells among the central core of epithelioid cells. Counterstained with Harris haematoxylin (×310).

antibodies, the lymphocytic subpopulations of normal human conjunctiva and found that the T cells were the preponderant cell type with the greatest density in the substantia propria of the forniceal region and with a slight excess of T suppressor cells over the T helper cells there. Bhan and coworkers[20] on the other hand stated that in diseased conjunctiva such as in ocular pemphigoid, vernal conjunctivitis, and Mooren's ulcer the helper/inducer cells formed a major component of the T cell population and only in graft-vs-host disease did the T suppressor/cytotoxic cells outnumber the T helper cells in the cellular infiltrate of the conjunctival specimen.

We did not have conventional histological sections of the conjunctival specimens to be compared with the frozen sections and not all the sections and stainings were fully successful. Epithelioid cell granulomas were found in only three specimens which could definitely be regarded as being of sarcoid origin. However because all patients had an active multisystem sarcoidosis we presume that the composition of the immunocompetent conjunctival cell population of all specimens had been modified by the sarcoid reaction.

In the present nine sarcoid conjunctival specimens the T cells represented the main cell type, and among them the mean ratio of the T helper/inducer to T suppressor/cytotoxic cells was nearly fourfold. This finding indicates that the T helper cells are actively involved in the local cell-mediated immune reaction in the conjunctiva in sarcoidosis, and this is in agreement with the findings of others concerning pulmonary,[7, 8] skin,[10, 11] peripheral lymphonodal,[9, 12, 21] intrabulbar,[22] and conjunctival[8, 14] sarcoidosis. It can be suggested that in active sarcoidosis the conjunctiva like any other tissue can be a target site for the T helper cells to be compartmentalised. Agni and coworkers[14] in their series of 26 sarcoid conjunctival specimens from patients with a duration of sarcoidosis from 6 months to 18 years counted a much higher excess of T helper cells over T suppressor cells ranging from seven to 36-fold. This indicates that their patients had a more active sarcoidosis than our patients at least at the conjunctival level. However their method of counting the positive cells as well as their selection of patients may have differed from ours.

Bronchoalveolar lavage studies have shown that lung T lymphocytes mainly T helper/inducer cells release lymphokines such as macrophage migration inhibitory and various macrophage activating factors that interact with monocytes/macrophages to assist in the formation of a granuloma.[6, 8] The same cascade of events can be supposed to occur in the affected conjunctiva in active sarcoidosis. In our sarcoid conjunctival specimens the number of macrophages was only a third of that of T cells. Apparently macrophages do not belong to the normal cellular population of the conjunctiva,[19] and they are only secondarily drawn to the site of the conjunctival immune reaction. In contrast the pulmonary alveolar spaces of healthy non-smoking persons harbour mainly macrophages (more than 90% of cells in bronchoalveolar washings).[8] Thus it is conceivable that in the alveolar tissue there is readiness to initiate the formation of granulomas. In the conjunctivae the granulomas possibly develop slowly under the influence of the continuous presence of antigen(s). If the assumed antigen exposure at the conjunctival level does not last long enough the local cell-mediated immune reaction may be extinguished before full evolution of granulomas takes place. This hypothesis is supported by the study of Agni and coworkers[14] who have shown the evolution pattern of the sarcoid conjunctival reaction from a small collection of macrophages surrounded by a few T helper lymphocytes to multiple aggregates of epithelioid and giant cells and a varying number of lymphocytes constituting dense cellular infiltrates.

Interestingly all inflammatory cell subtypes in the specimens from our newly diagnosed patients were more numerous on average than those in the specimens from our chronic patients. The increase of all immunocompetent cell subtypes may belong to the initial and active phase of sarcoid conjunctival reaction. The same phenomenon has been demonstrated in early and active intraocular[22] and extraocular[11] sarcoidosis as well as other active cell mediated immune disorders, for example sympathetic ophthalmia,[23] and has been suggested to be a by-product of the complex chemotactic factors liberated at the reaction site. Marked HLA-DR positivity in the conjunctival specimens of our newly diagnosed patients is also in keeping with this idea. HLA-DR is a marker considered vital in initiating immune response and is found in macrophages, B lymphocytes, and activated T lymphocytes.[24] The excess of B cells in the conjunctival specimens from our newly diagnosed patients was especially high – 18-fold. This may result from the polyclonal activation of the B cells at the conjunctival level. A phenomenon comparable with this is demonstrated in active pulmonary sarcoidosis.[5]

In our chronic specimens there were mainly T cells with a mean excess of the T helper/inducer cells 5·7-fold over the T suppressor/cytotoxic cells in addition to macrophages and epithelioid cells concentrating in two cases in the granuloma areas. Consequently T helper cells seem to be essential both in the early and in the chronic conjunctival sarcoid reaction. We have shown previously[25] that conjunctival granulomas confirmed by a conventional histological method may remain at the same site for years. In those cases an equilibrium between T helper cells and T suppressor cells evidently has been achieved. Such an equilibrium possibly had been achieved in our patient 7 and 9. This steady state in chronic cases may also result in extinguishing the assumed initial polyclonal B cell activation with a consequent decrease of the conjunctival B cells. Long-term treatment with corticosteroids in three of five chronic cases may also have had a decreasing effect on all subtypes of conjunctival immunocompetent cells.

In conclusion our study demonstrates variations in the cellular components in the conjunctiva in recent onset and chronic sarcoidosis. We believe that sarcoid reaction in the conjunctiva is a dynamic process in which proliferation of the immunocompetent mononuclear cells precedes the stage of granuloma formation.

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FIFTY YEARS AGO

The Education of an Ophthalmic Surgeon

Many ophthalmic surgeons in Britain in the past have slipped into their particular niches fortuitously; and not only ophthalmic surgeons, for we remember the story of a young man waiting for an ophthalmic vacancy becoming eventually a distinguished obstetrician. This was a good many years ago; but when Brudenell Carter was appointed ophthalmic surgeon at St George's Hospital in 1870 it was settled that part of his hospital duties was to undertake the responsibility of the obstetrician's holiday work. This was no particular hardship, for as Carter had been in general practice until he was 40 years old he was quite competent to deal with straightforward or difficult cases of labour. Times have changed since then but we feel quite sure that those who have entered specialists' work without *any* experience of general practice first have missed a great deal. The converse, when an elderly general practitioner gives up general practice for ophthalmology, is not at all common; but has occurred in a few instances.
Br J Ophthalmol 1942; 26: 75

British Journal of Ophthalmology, 1992, 76, 107–108

MINI REVIEW

Endothelin: a new vasoactive ocular peptide

The retinal vasculature and autoregulation

The tone of most blood vessels in the body is regulated by means of the autonomic nervous system. The vasculature of the human retina, however, lacks extrinsic innervation even though autonomic receptors are present in the walls.[1] Vessel calibre and local blood flow are normally regulated by non-nervous mechanisms intrinsic to the retina. This autoregulatory process helps preserve a uniform retinal blood flow in the presence of a variable perfusion pressure and matches it to tissue oxygen and metabolic requirements.[2] The failure of autoregulation is an important and often early feature of retinal vascular disease and can be influenced in some instances by laser photocoagulation, for example diabetic retinopathy.[3]

Retinal pericytes

The effector cells in autoregulation are the vascular smooth muscle (VSM) cells, and their tone and active contraction control vessel diameter, blood flow, and tissue oxygen levels. In most mammalian circulations the precapillary arteriolar sphincters play a pivotal role in the control of blood flow to the capillary bed.[4] However these strategic collars of smooth muscle cells are not a feature of the retinal circulation in the primate eye. There is now a considerable body of evidence to suggest that retinal pericytes, which are the microvascular correlates of VSM cells, are responsible for changes in retinal capillary tone and local blood flow. Pericytes have been shown to contain the smooth muscle isoforms of both actin and myosin[5] and cGMP dependent protein kinase,[6] thus providing further documentation of morphological and biochemical similarities to smooth muscle and for a contractile role. Pericytes have also been shown to deform substrata in vitro[7] demonstrating that these cells have the potential to contract and exert significant amounts of traction in vivo.

Endothelin 1: an endothelium-derived vasoactive agent

It is now known that vascular endothelium can influence vascular tone and blood flow by the production of potent vasodilators[8] and vasoconstrictors[9] which affect the underlying smooth muscle. In 1988 Yanagisawa *et al* isolated and characterised an endothelium-derived 21 amino acid vasoconstrictor polypeptide which they termed endothelin.[10] Endothelin is a member of a family of peptides arising from three preproendothelin species which, after proteolysis, yield three isoforms termed endothelin 1, 2, and 3 (ET1, ET2, and ET3).[11] ET1 is the most potent constrictor known of large and small vessels particularly those of the kidney and has major biological effects on VSM cells[12] and the renal mesangial cell which is a pericyte.[13] The mechanism of action of ET1, which has been extensively studied in the renal mesangial cell, suggests that ET1 induced contraction occurs as a result of pharmacomechanical coupling to ET1 receptors with activation of the phosphoinositide cascade involving phospholipase A_2 to produce prostaglandins E_2, $F_2\alpha$ and thromboxane A_2.[14] ET1 immunoreactivity has been demonstrated in the vasculature of a wide variety of tissues including brain indicating widespread presence of the peptide.[15] The identification of ET1 mRNA in the neurons of the hypothalamus[15] has suggested a neuromodulatory function for this peptide and stimulated interest in its potential role in ocular tissues.

ET1 and ocular tissues

ET1 binding sites have been demonstrated in the ciliary body and the peptide, when injected intracamerally, has been shown to increase outflow facility suggesting that it may be involved in the physiological control of ciliary body function and aqueous outflow.[16] Recent studies have shown that ET1 stimulates the release of arachidonic acid and prostaglandins in rabbit iris smooth muscle with activation of phospholipase A_2.[17] The capacity of ET1 to increase eicosanoid production by uveal tissue is an indicator of its potential as a mediator of vascular responses in inflammation.

ET1 and retinal vascular autoregulation

It is known that ET1 can augment the production of endothelium derived nitric oxide and prostacyclin both of which are potent vasodilators,[18] allowing vascular endothelium to exercise molecular control over vessel tone and diameter, thereby regulating local blood flow. It has recently been shown that cultured retinal capillary endothelial cells secrete ET1 and corresponding pericytes bear receptors for this peptide,[19] suggesting the presence of a specific interactive system for the regulation of retinal capillary blood flow in a circulation which shows no evidence of extrinsic innervation. ET1 exerts its maximal effect at the abluminal aspect of the endothelium/smooth muscle/pericyte interface and, accordingly, intravenously administered ET1 does not cause an increase in cerebrovascular resistance owing to the presence of the blood brain barrier.[20] A similar effect would be expected in the retinal circulation and indeed it has been shown that isolated preparations of 'retinal branches of bovine short posterior ciliary arteries' exhibit rapid, reversible, and repeatable contractions in response to abluminally applied ET1.[21] In contrast ET1 induced contractions in vascular preparations of human isolated resistance vessels and cat middle cerebral arteries are long-lived, relaxation is slow, and the vessels are refractory to further ET1 stimulation.[22] The reasons for this disparity are unclear as vascular smooth muscle cells, renal mesangial pericytes,[22] and bovine retinal capillary pericytes (BRCP)[24] respond in vitro to ET1 stimulation by prolonged contraction which is maintained for periods of up to 2 hours after removal of agonist. Moreover ET1 binding studies on BRCP have revealed that the binding sites are of high affinity with equilibrium dissociation constants in the nanomolar range.[19] The binding is therefore not easily reversible so accounting for the prolongation of the observed contractile response. The easily reversible contraction seen in posterior ciliary vessels in response to ET1 in the above mentioned study suggests the presence of a subtype of receptor rather than the receptor to ET1. The significance of such findings is open to speculation and indicates a differential responsiveness of the various circulatory beds to ET1.

ET1 and hyperglycaemia

Recent studies have shown that vascular endothelium maintained in vitro under conditions of hyperglycaemia simulating diabetes releases less ET1 than under normoglycaemic conditions,[25] and pericytes cultured in high levels of glucose exhibit reduced contractility to ET1 stimulation.[26] These observations suggest that ET1 production by vascular endothelium and the contractile response of the underlying effector cells may be flawed in diabetes and possibly implicated in the pathogenesis of diabetic microangiopathy.

ET1 and retinal vascular endothelial cell-pericyte responses

Endothelial cell-pericyte interactions are now considered at least in part to be responsible for the biological control of endothelial cell proliferation as shown by electron microscopic studies of growing blood vessels in healing wounds,[27] and in experimental choroidal neovascularistion.[28] There is a growing body of evidence that endothelial cells and pericytes influence each other's replicative and biosynthetic behaviour,[29] and co-culture of these cells results in activation of transforming growth factor β (TGFβ) which in turn inhibits endothelial cell proliferation.[30] TGFβ itself can cause increased transcription of ET1 mRNA showing that biofeedback mechanisms exist allowing these growth factors to influence each other's production and participate in cellular interactions.[31] As ET1 is known to have mitogenic effects on retinal pericytes,[24] it is interesting to speculate that activation of TGFβ in vivo can in turn increase the expression of ET1 mRNA thereby influencing pericyte replication, maintenance, and health. The complexity of such interactions involving growth factors such as ET1 and TGFβ has major implications in the pathophysiology of diseases such as diabetes and hypertension where there may be a derangement in endothelial cell-pericyte interactions with consequent effects on the function of the microcirculation. The study of retinal vasculature and retina derived growth factors should improve our understanding of disease pathogenesis and pave the way for the development of better therapeutic modalities.

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CASE REPORTS

Exudative retinal detachment and posterior scleritis associated with massive scleral thickening and calcification treated by scleral decompression

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Abstract

A 66-year-old man presented with massive bilateral scleral thickening and calcification associated with a unilateral exudative retinal detachment which did not respond to systemic anti-inflammatory agents including steroids and cyclophosphamide but improved with scleral resection. This patient shows the features of both posterior scleritis and the uveal effusion syndrome, providing further evidence for the role of a thickened sclera and interference with the trans-scleral flow of fluid in the formation of such an exudative retinal detachment.

We report a case of bilateral massive scleral thickening and calcification associated with a unilateral exudative retinal detachment which responded to scleral resection. This resulted in an improved visual acuity which has been maintained for 4 years. This case shared many of the features of both posterior scleritis and the uveal effusion syndrome, and provides support for the hypothesis that the thickened abnormal sclera has a role in the formation of the subretinal fluid.

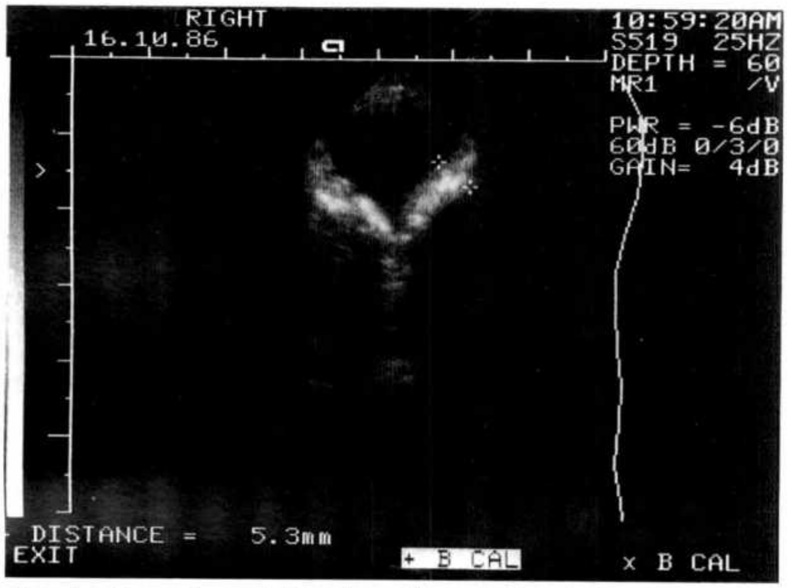

Figure 1A B-scan ultrasound of the right eye. The grossly thickened sclera measures 5·3 mm (between callipers).

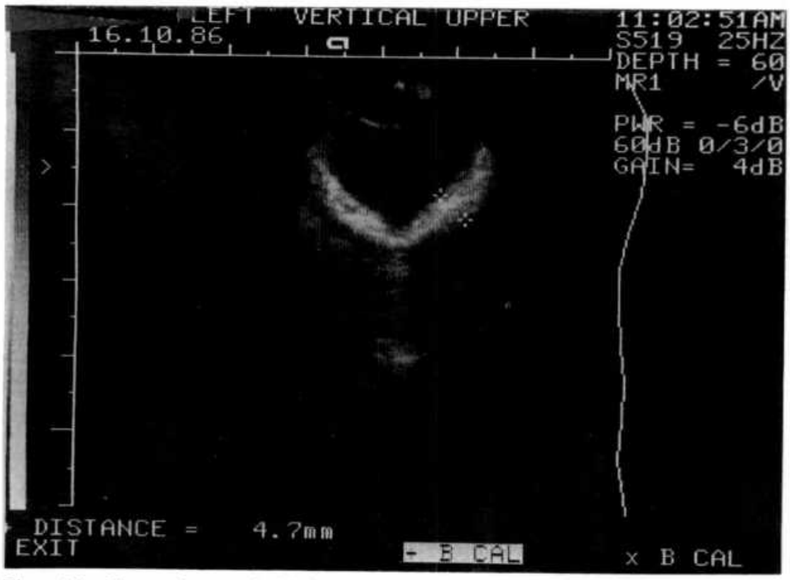

Figure 1B B-scan ultrasound of the left eye. The sclera measures 4·7 mm (normal 1·1–1·8 mm).

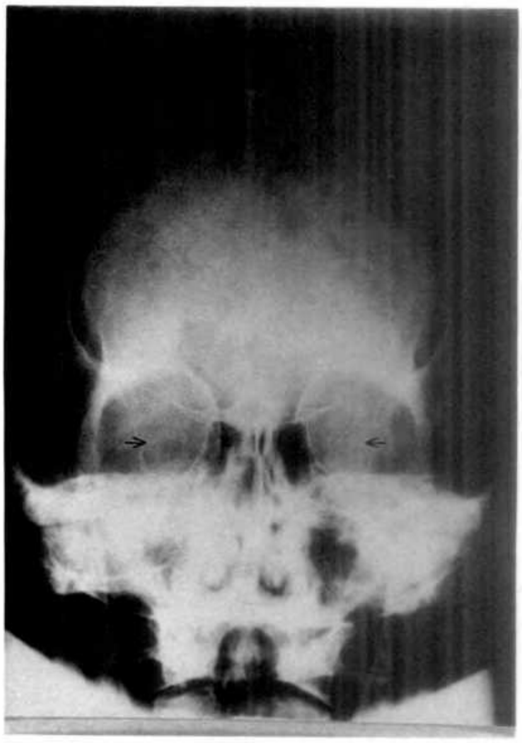

Figure 2 Plain anteroposterior skull x ray. Dense shadowing of the calcified sclera in the orbits (arrowed) is seen.

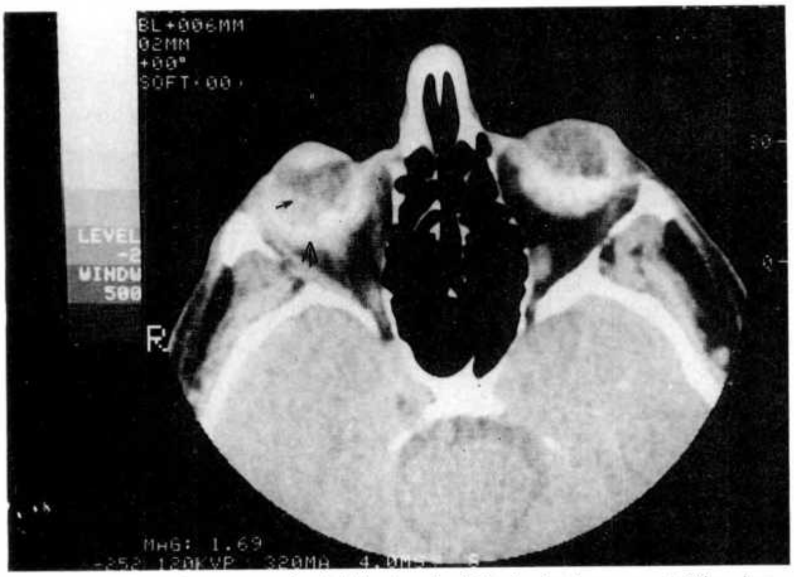

Figure 3 CT scan shows gross scleral thickening of calcific density (large arrow). There is a shadow representing the exudative retinal detachment in the right eye (small arrow).

Case report

A 66-year-old man was referred to the scleritis clinic 3 months after noticing decreased visual acuity in both eyes, worse in the right. He had been seen 12 years previously with red sore eyes but no diagnosis had been made and no treatment given. His medical history was of confirmed osteoarthritis and previous surgery for peptic ulceration.

On ocular examination at presentation the visual acuity of the right eye was counting fingers and the left 6/18. Both eyes were red with episcleral vascular dilatation. The anterior sclera was visibly thickened with a cream coloured lumpy appearance most noticeable at the equator and tapering to the limbus. There was a slight aqueous flare in the right eye and a few cells in the anterior vitreous. The choroidal vascular pattern appeared normal. However the choroid was thickened by yellow nodular infiltrates and the retina showed marked clumping of pigment in both eyes. In the right eye there was an exudative retinal detachment with shifting subretinal fluid.

Ultrasound showed a grossly thickened posterior sclera (Fig 1A and 1B). A ring of calcification was found on the plain skull *x* ray (Fig 2). These features were demonstrated both on the computed tomography (CT) scan (Fig 3) and the magnetic resonance image (MRI) (Fig 4).

Haematological investigation revealed a mild iron deficiency anaemia and a paraproteinaemia which was quantified showing IgGλ 17 g/l and IgAκ 12 g/l. Urinary Bence Jones proteins showed λ light chains. Bone marrow aspirates did not reveal evidence of myeloma.

An inflammatory aetiology was suspected and, after initial unsuccessful treatment with flurbiprofen, he was treated with pulsed methyl prednisolone 500 mg and cyclophosphamide 500 mg. Following this, treatment was continued with oral prednisolone 20 mg daily and cyclophosphamide 50 mg twice daily. Additional treatment with oral iron and cimetidine was given. One month later however the clinical findings were unchanged and the iron deficiency had resolved.

Surgical exploration of the right eye was undertaken (PGW). The vortex veins were identified as thread like and non-perfused. Two wedges of sclera were excised in the inferonasal and inferotemporal quadrants and the choroid was exposed.

The retina has remained flat since the operation except for a small area inferiorly which has not altered in 4 years. The visual acuity has been stable at 6/36 and 6/18, right and left respectively.

Histology of the resected material showed dense fibrous tissue with small zones of hyalinisation and calcification. There was some irregular inflammatory cell infiltrate consisting largely of lymphocytes and plasma cells (Fig 5A and B). There was no evidence of myeloma.

Discussion

This patient shared many of the features of posterior scleritis and the uveal effusion syndrome.

Posterior scleritis usually presents with severe unilateral pain and decreased vision. Thickening of the coats of the eye are seen in the active stage[1-5] on ultrasound. Other features are choroidal folds, optic disc swelling, retinal pigment epithelial changes, and exudative retinal detachments.[3-6] It most frequently occurs in middle aged women[1,7] when it is often associated with connective tissue disease or in young patients who are rarely found to have systemic disease. It may go unrecognised if it is pain free.[8,9] The condition often responds to nonsteroidal anti-inflammatory drugs (NSAIDS) or to systemic treatment with steroids and immunosuppressives.[10,11] Management with surgery is not described.

The uveal effusion syndrome presents with a painless decrease in vision. An annular choroidal detachment with exudative retinal detachments are found on examination.[2,12-14] This condition is bilateral but may be asymmetrical. The sclera is

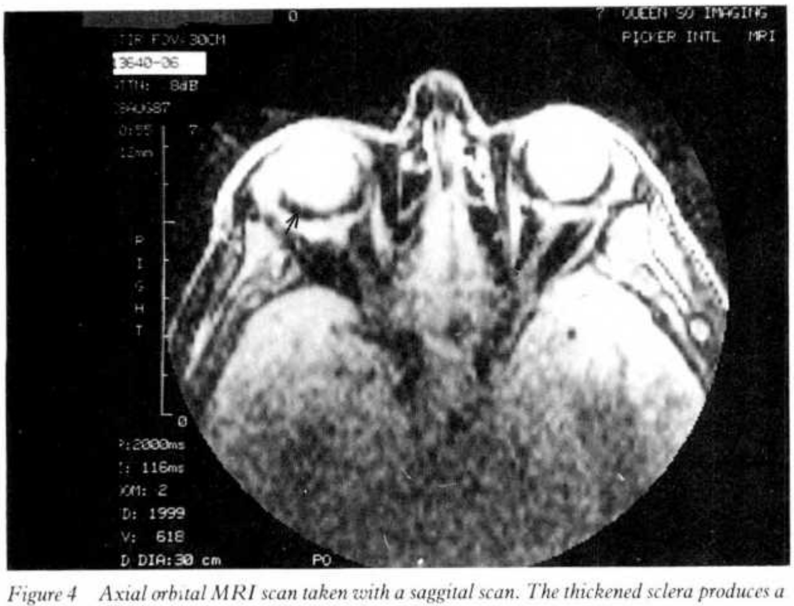

Figure 4 Axial orbital MRI scan taken with a saggital scan. The thickened sclera produces a low image (black arrow).

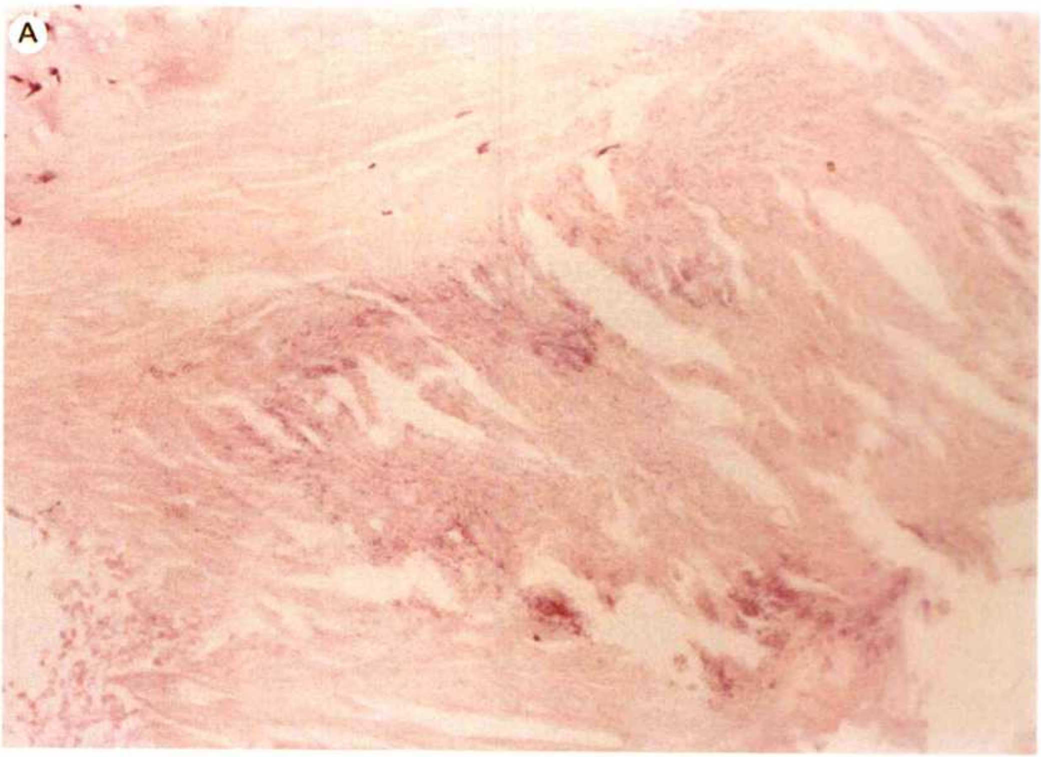

Figure 5A Low power histopathological section (H and E) showing dense fibrous tissue with small zones of hyalinisation and calcification.

frequently thickened[15 16] and may be abnormal[17] but inflammatory cells have not been found histologically.[18] Anatomical variation or occlusion of the vortex veins is described. The uveal effusion syndrome typically occurs in healthy males. Resolution of the symptoms with systemic treatment including steroids is rare; however these patients respond to scleral surgery[4] such as vortex vein decompression with scleral incisions and partial thickness sclerectomies.[12 13 17 19 20]

An exudative retinal detachment may occur when normal movement of fluid from the subretinal space to the suprachoroidal space and out of the eye via the vortex veins is disturbed.[21 22]

The retinal pigment epithelium has a mechanism for pumping water but not colloid[23] resulting in a protein rich subretinal fluid. In the uveal effusion syndrome there is a high protein concentration in the subretinal fluid.[24]

Brubaker and Pederson[25] emphasise the importance of scleral permeability to water and colloid in maintaining hydrostatic and osmotic gradients for the apposition of choroid to sclera. When ocular inflammation is present there is excess transudation of colloid from the choroidal

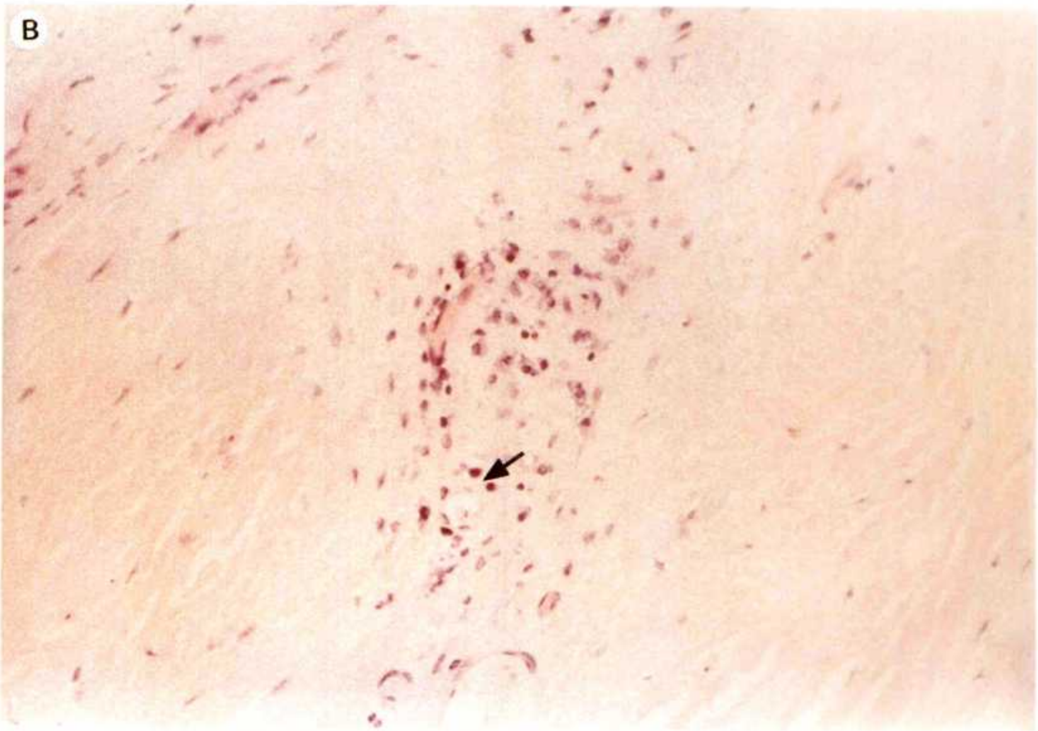

Figure 5B Higher powered view showing a few scattered inflammatory cells (arrow).

vasculature into the extracellular compartment which can only leave via bulk flow through the sclera.

Our patient has a 12 year history of red uncomfortable eyes. Chronic inflammation was found on histological sections with calcification which is likely to have occurred as a dystrophic event.[26]

It appears that the physical signs observed in our patient were the result of several factors. There was inflammation leading to scleral thickening, calcification, and vortex vein occlusion with consequent inability to transfer fluid and colloid through the sclera. The abnormal pigment epithelium allowed colloid and fluid to be retained in the subretinal space. Immunosuppressive treatment was insufficient to reverse this. However scleral resection to allow trans-scleral flow of suprachoroidal and subretinal fluid was successful

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Transient loss of peripheral vision as the presentation of left atrial myxoma

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Abstract

A 42-year-old man developed transient loss of vision in both eyes. On echocardiography to investigate a systolic murmur and determine the potential source of emboli, a large left atrial myxoma was diagnosed. This was removed successfully leaving no visual or neurological deficit.

Case report

A 42-year-old builder presented with sudden loss of vision in the lower temporal quadrant of his right eye lasting for 10 minutes with full recovery. A similar episode lasting 5 minutes affected the upper temporal quadrant of the left eye the next day. He described transient pain in his knuckles at the same time that he was aware of blurred vision. Direct questioning established a history of rheumatic fever at the age of 5 years.

On examination he was an obese male Caucasian with no jaundice, cyanosis, purpuric rashes, splinter haemorrhages, or digital clubbing. His pulse was 80 and regular, and his blood pressure was 120/90 mm Hg. In addition to normal first and second heart sounds he had a harsh apical systolic murmur. All peripheral pulses were palpable and his chest was clinically clear. The central nervous system was normal. His visual acuity was 6/5 without correction in both eyes and the visual fields were full. Fundus examination showed no features of embolism or retinal ischaemia. Investigations included a chest *x* ray, electrocardiogram, erythrocyte sedimentation rate, full blood count, lipid profile, serum electrolytes and urea, blood cultures, and thyroid function tests, which were all normal. Urine analysis revealed blood ++++ and protein ++ but midstream urine microscopy and culture were negative. Carotid Doppler echography showed a higher than normal peak systolic frequency in the left external carotid artery. His echocardiogram demonstrated a large mobile mass prolapsing through the mitral valve (Fig 1). A pedunculated cylindrical myxoma, 15 cm long, was surgically removed from the left atrium (Fig 2).

Two months later the visual acuity remained normal at 6/5 in each eye. Fundus examination revealed several minute superficial retinal haemorrhages just behind the ora serrata in both eyes. A small choroidoretinal scar was identified in the mid-periphery of the retina at the 10 o'clock meridian in the right eye.

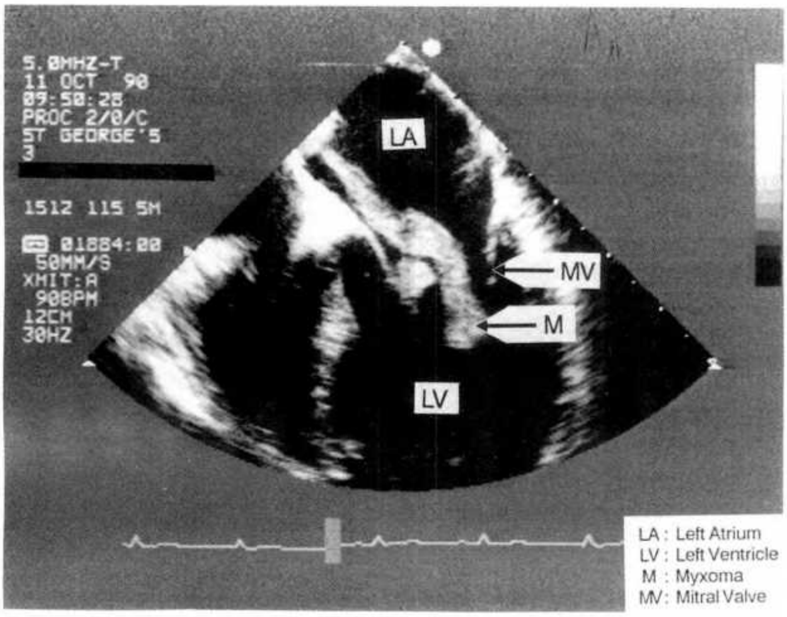

Figure 1 Transoesophageal echo image of the parasternal long axis of the heart. The atrial myxoma (M) is seen prolapsing through the mitral valve (MV) into the left ventricle (LV).

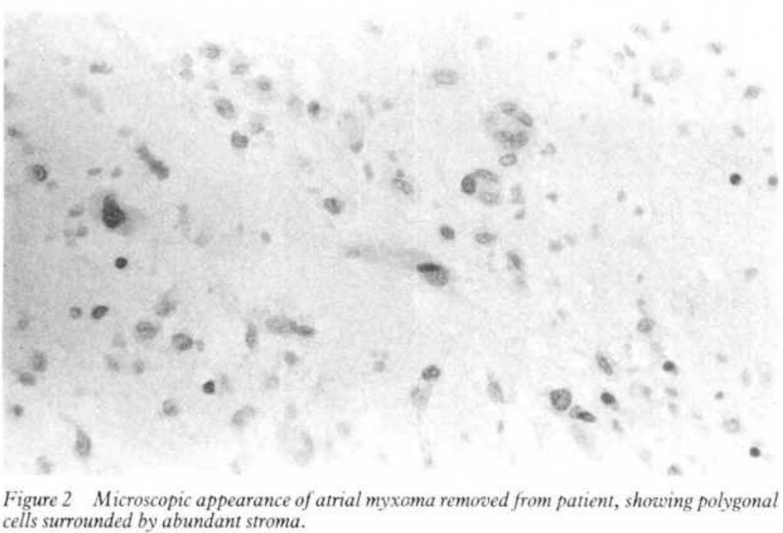

Figure 2 Microscopic appearance of atrial myxoma removed from patient, showing polygonal cells surrounded by abundant stroma.

Discussion

Primary cardiac tumours are themselves very rare, and of these the commonest is atrial myxoma (50%). Though they are said to be benign tumours metastatic deposits have been widely reported. Grossly, myxomas are soft, polypoid, pale, lobulated masses often attached by a stalk to the atrial septum close to the foramen ovale. Seventy five per cent of cardiac myxomas arise from the left atrium.[1,2] Microscopically, round, polygonal, or stellate cells are seen surrounded by abundant loose stroma rich in acid mucopolysaccharides. Atrial myxomas have been described in all age groups, with the greatest incidence between 30 and 60 years. The organ affected by embolism governs the mode of presentation of atrial myxoma and its severity. Retinal embolism from atrial myxoma is rare.[3,4] Transient peripheral visual loss in association with atrial myxoma has not been described previously. The most frequent sites for systemic embolism are the brain and kidneys.[5] Renal tissue damage would explain the results of urine analysis in our patient.

The auscultatory signs of atrial myxoma consist of variations in the intensity of the first and second heart sounds, while possible murmurs vary from systolic and late diastolic to pansystolic murmurs.[6] Features associated with atrial myxoma include chest pain, pyrexia, weight loss, arthralgia, and fatigue. Other abnormal findings include anaemia, polycythaemia, an elevated ESR, and raised plasma globulin levels. However, biochemical and haematological tests are not specific in establishing the diagnosis of atrial myxoma, as they are abnormal in only half of all those patients who present with constitutional symptoms.[7,8] This patient's only specific constitutional symptom was transient knuckle pain. His positive clinical findings were an apical systolic murmur, haematuria, and proteinuria. The abnormal flow pattern in the left external carotid artery showed very little improvement after surgical intervention. In retrospect the history of rheumatic fever was probably incorrect as atrial myxoma may mimic its clinical presentation.

The absence of early fundus signs is consistent with the transience of the visual symptoms in this patient. The likely cause of transient branch retinal arteriolar obstruction in this case is fibrin platelet emboli rather than myxoma fragments. Fundal changes are not always identified, even in cases presenting with central retinal artery occlusion.[9] We ascribe the subsequent appearance of fundal changes in our patient to retinal ischaemia at the time of open heart surgery.

The definitive diagnosis of atrial myxoma is made by echocardiography. Small myxomas remaining in the atrium during systole may be missed using a transthoracic approach alone. Therefore it is now usual to combine transthoracic and transoesophageal two-dimensional studies, both to establish the precise diagnosis and to determine the best surgical approach.[10,11]

Conclusion

The diagnosis of atrial myxoma is difficult, due to the rarity of the condition, its variable clinical presentation and physical signs, and the lack of specific laboratory findings. Although retinal embolism from atrial myxoma is uncommon, full cardiac screening is justifiable with ocular symptoms alone, even in the absence of neurological signs. With the early diagnosis of atrial myxoma it is now possible to resect the tumour, thereby avoiding the onset of a massive stroke or death, and allowing full recovery for the patient.

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Delleman syndrome: a case report and review

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Abstract

A case of oculocerebrocutaneous syndrome is presented, to our knowledge the first to be reported in West Bank and Gaza. The child was of consanguinous parents. The clinical features of orbital cyst, periorbital cutaneous malformations, and cerebral malformations are described, together with a brief review of previous reports. The need for neurological follow-up of these cases is emphasised.

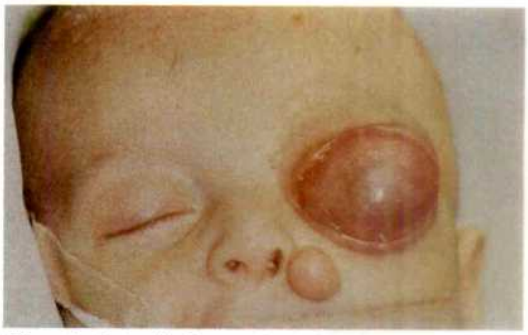

Figure 1 Left orbital cyst and periorbital skin tag.

The oculocerebrocutaneous syndrome was described by Delleman and Oorthuys in 1981[1] who reported on two patients with congenital orbital cysts, cerebral malformations, and focal skin defects. Further cases have since been described.[2-4] We present an infant with this syndrome of consanguinous parents, a feature not previously reported. The oculocerebrocutaneous syndrome is not widely recognised among ophthalmologists and may well be less rare than hitherto thought.

Case report

This female infant is the third child of healthy consaguinous (first cousin) Palestinian parents aged 27 (mother) and 31 (father) with two other normal children. Pregnancy and home delivery were uncomplicated. A the age of 2 h, the infant presented to St John Ophthalmic Hospital with a left orbital mass.

A large translucent cyst protruded from the left orbit with no visible ocular tissue (Fig 1). A coloboma was present at the junction of the medial and central thirds of the left upper lid. The right eye was normal. A large skin tag was present below the left orbit; smaller appendages involved the left side of the nasal septum and left lower lid margin. Pigmented areas of very thin dermis and small pitted skin lesions were present above the left ear and on the forehead.

The infant weighed 2800 g, measured 47 cm with a head circumference of 31 cm (below the 3rd percentile). Examination of the respiratory, cardiovascular, genitourinary, and neurological systems was normal. Karyotype was XX, 46.

Computed tomographic (CT) scan showed a cystic left orbital mass with no intracranial communication and left cerebellar atrophy. At surgery clear fluid was aspirated from the cyst which was freed from the surrounding conjunctiva and periorbita and excised together with solid tissue lying deep to the cyst. Following conjunctival closure a conformer was inserted and maintained in the orbit with a central tarsorrhaphy.

Histology showed a severely disorganised microphthalmic globe with orbital cyst. The

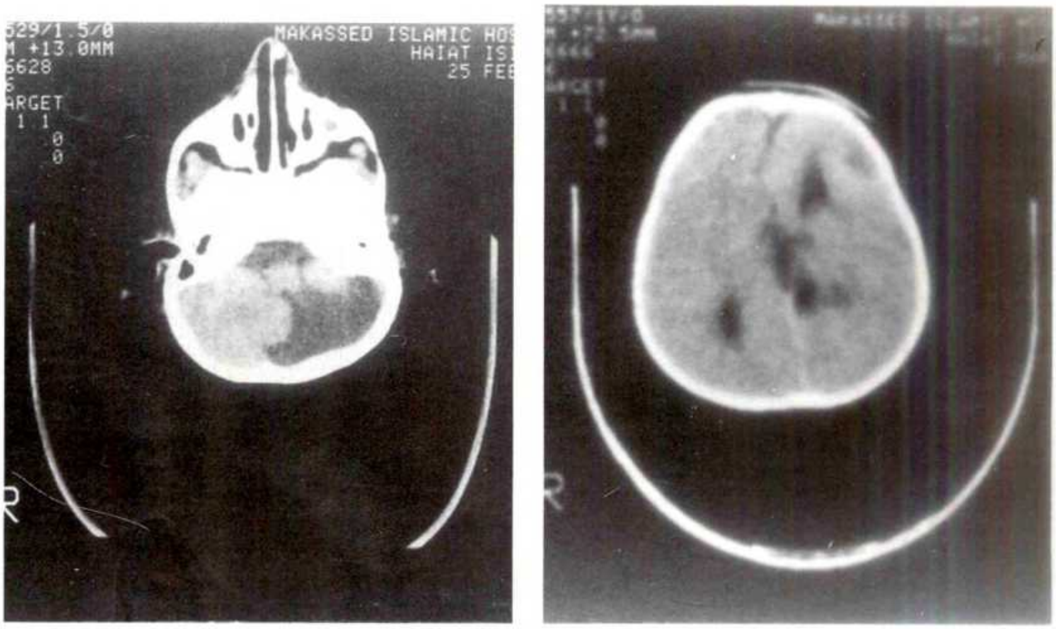

Fig 2A

Fig 2B

Figure 2 CT scan showing left cerebellar atrophy (A) and cystic defects (B).

incompletely formed eye was represented by dysplastic retinal tissue with rosette formation, ciliary muscle, pigment epithelium, and some scleral condensation of fibrous connective tissue. Calcified lens material and islands of cartilaginous metaplasia were also present. The cyst wall consisted of neuroepithelium and glial tissue.

At 16 months moderate developmental delay was noted. A repeat CT scan showed multiple hemispheric cystic defects in addition to the previously noted left cerebellar atrophy (Fig 2).

Discussion

Al-Gazali *et al*[5] reviewed five previously published and four new cases. However one of the new cases did not have cerebral lesions, casting doubt as to whether it should be included. There are reports in the literature which most probably represent unrecognised cases of the syndrome.[6,7]

The most obvious feature is the presence of an orbital cyst which may be bilateral (three cases) and can be associated with microphthalmos (four cases) and/or eyelid coloboma (four cases). The cerebral malformations noted were multiple cystic spaces in the brain which in four cases were accompanied by agenesis of the corpus callosum. Psychomotor retardation and convulsions were present in seven cases. Cutaneous manifestations include the presence of accessory facial skin tags in the periorbital area and foci of dermal hypoplasia seen as pink or pigmented areas where subcutaneous fat prolapses through atrophic dermis.

Our case shows the features of the syndrome described by Delleman and Oorthuys. Detailed histological examination of the cyst was performed in only one previously reported case.[4] The pathological findings in our case confirm the hamartomatous nature of the cyst with primitive neuroectodermal, retinal, and glial tissue.

Lesions involving orbital, cerebral, and facial structures point to a disruption of embryonic development at a very early stage. Microphthalmos with cyst is related to incomplete closure of the embryonic fissure, normally occurring at 5–6 weeks,[8] with cystic extension of neuroretinal tissue through the defect into the orbit.[9] Fusion of the maxillary processes with the lateral nasal and globular processes to form the nose, mouth, and lid folds occurs at the same stage. The distribution of accessory facial skin tags along the lines of fusion of the facial buds suggests a similar problem with closure of these embryonic furrows.[6] Likewise, agenesis of the corpus callosum may be considered as a failure of commissural fibres to link up in the midline.

The possibility of autosomal recessive inheritance is raised by the parental consanguinity found in our case, a feature not previously reported. Ophthalmic and general examination of the parents and both siblings were normal. To date there have been no reports of any affected siblings. The sex ratio for this condition so far is male:female 6:4.

Chromosomal aberrations such as trisomy 13 (Patau's syndrome), trisomy 18 (Edward's syndrome) and chromosome 18 deletion defect may give rise to microphthalmos together with facial and neurological abnormalities.[10] Accessory skin tags are a feature of Goldenhar's syndrome in which upper eyelid colobomas and microphthalmos may also occur. However in Goldenhar's syndrome epibulbar dermoids are the more typical ocular feature, the skin tags are found in the preauricular rather than the periorbital region and cerebral cystic defects are not part of the clinical picture. Microphthalmos, coloboma and focal dermal hypoplasia may occur in Goltz syndrome[11] but other characteristic abnormalities include polysyndactyly and poor dentition. Goltz syndrome is inherited as an X-linked dominant condition occurring only in females as it is lethal in males. Ultrasound and CT may be helpful in excluding meningoencephalocele or tumour.[12]

True anophthalmia is extremely rare; more commonly some attempt at eye formation gives rise to a congenital cystic eye or microphthalmos with or without cyst. The cyst may be sufficiently large to obscure the microphthalmic eye. Depending on size the orbital cyst may be either left alone, aspirated, or excised. Aspiration may need to be repeated as reaccumulation of fluid is not uncommon and may occur rapidly.[7] Excision of the cyst is facilitated by initial aspiration following which it is readily dissected free of the conjunctiva and periorbita. As much conjunctiva as possible must be preserved and frequent introduction of increasingly larger conformers is required to avoid socket contracture.

The need for neurological follow up is borne out by the psychomotor deficit documented in our patient. Progression of clinical and/or CT findings was noted in at least three of the previously reported cases[1,3,5] one of whom died with hydrocephalus. Ophthalmologists should be aware of the possibility of cerebral malformations in patients with congenital orbital cysts and skin appendages.

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Pituitary adenoma presenting as the Foster-Kennedy syndrome

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Abstract

A 27-year-old man presented to the casualty department with visual failure. Clinically he demonstrated the Foster-Kennedy syndrome. Computed tomography revealed a large space-occupying lesion which was subsequently shown to be a pituitary adenoma. The literature is reviewed and possible mechanisms of the Foster-Kennedy syndrome are discussed.

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The Foster-Kennedy syndrome although not a common phenomenon has been described in association with a wide variety of intracranial pathologies. We present here the first case of the Foster-Kennedy syndrome secondary to a pituitary adenoma.

Case report

A 27-year-old man presented to the casualty department of an ophthalmic hospital complaining of visual failure. The vision in his right eye had been declining slowly over the preceding 4 years but over the week prior to presentation it had fallen precipitously resulting in complete blindness in this eye. The vision in the left eye had also deteriorated over the preceding week together with the onset of frontal headaches associated with nausea and vomiting. There were no other symptoms but his general practitioner had noted the presence of a right convergent squint.

On examination he was generally well, apyrexial, alert, and orientated. Visual acuities were no perception of light on the right, hand movements on the left. There was a right relative afferent pupillary defect and fundal examination revealed optic atrophy on the right and marked papilloedema on the left (Fig 1). There was venous congestion and absent venous pulsation in both eyes. In addition he had limitation of lateral rectus function bilaterally, more pronounced on the right, and limitation of upward gaze. There were no other focal or generalised neurological signs. He was therefore diagnosed as having the Foster-Kennedy syndrome.

Computed tomography (CT) scan of the brain showed a large lobulated mass arising in the midline from near the sella turcica and extending behind the dorsum sellae into the anterior part of the posterior cranial fossa indenting the upper pons and filling the interpeduncular cisterns. It also extended upwards into the right frontal lobe distorting the ventricular cistern and obliterating the anterior horn of the lateral ventricle. There were also some areas of cystic cavitation (Fig 2).

The patient was transferred to the National Hospital for Neurology and Neurosurgery where a large right frontal tumour was excised via a frontal craniotomy. Frozen section suggested a pituitary adenoma and formal histology confirmed this and showed positive staining for prolactin. Serum prolactin was measured at 39 000 megaunits/l (normal up to 480 megaunits/l). He was subsequently started on bromocriptine and by 3 weeks postoperatively the prolactin level had fallen to 600 megaunits/l.

At 4 weeks post operation the right visual acuity remained no perception of light but the left had recovered to 6/6 unaided albeit with only a 5° central field. The lateral rectus palsies had greatly improved. Fundal examination now revealed bilateral optic atrophy.

Discussion

The syndrome described by Foster-Kennedy in 1911,[1] characterised by 'the occurrence of true retrobulbar neuritis with the formation of a central scotoma and primary optic atrophy on the side of the lesion together with concomitant papilloedema in the opposite eye', had been reported previously by Gowers[2] and Paton.[3] It has since been associated with a diverse selection of pathologies including frontobasal tumour,[1,4–7] abscess of the frontal lobe,[1] meningioma of the olfactory groove,[1,2,8–11] falx[12] or sphenoidal wing,[5,13–15] craniopharyngioma,[16] plasmacytoma,[17] nasopharyngeal angiofibroma,[18]

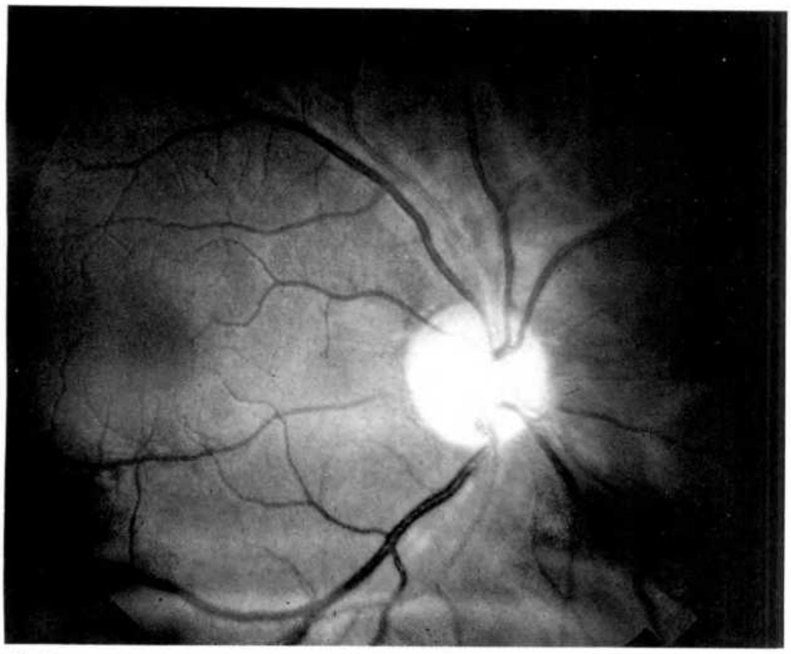

Fig 1A

Figure 1 Optic discs at presentation showing (A) right optic atrophy and (B) left papilloedema.

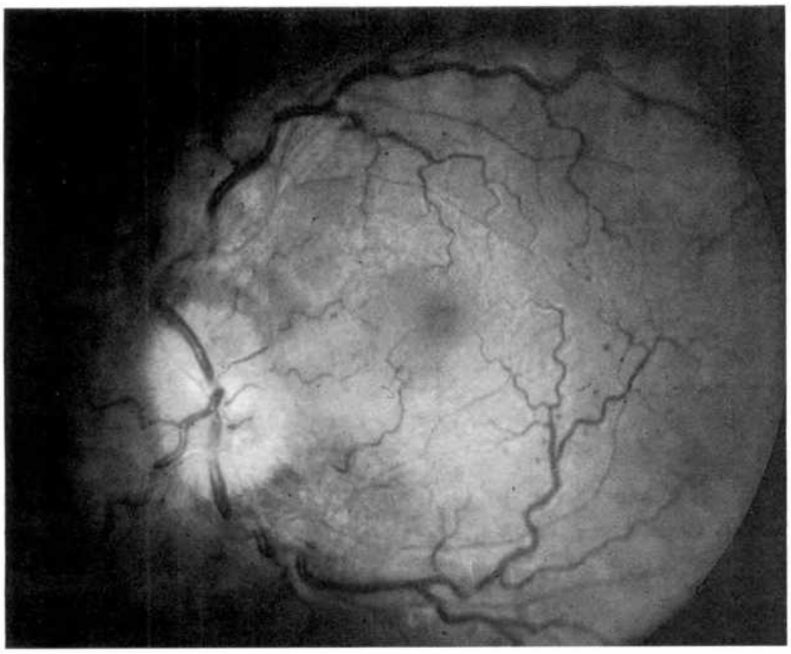

Fig 1B

neuroblastoma,[19] aneurysms,[20] and other diverse intracranial lesions.[21] We believe this to be the first reported case of the Foster-Kennedy syndrome occurring in conjunction with a pituitary adenoma.

The Foster-Kennedy syndrome is not a common entity. Tonnis found only 28 cases in a series of 3033 intracranial tumours,[22] Von Wowern four out of 686 frontal tumours,[5] Huber one of 46,[6] and Cushing seven of 29 olfactory groove meningiomas.[7] This represents an overall incidence of less than 1%. Only 37 cases of the Foster-Kennedy syndrome have been completely documented between the years 1909–89 all but one with evidence of an intracranial mass.[18] Anosmia is often included in the syndrome but its presence has not been universally reported.[11] In none of these cases was the mass shown to be a pituitary adenoma although meningiomas arising from the tuberculum sellae have been described.[23] The mechanism by which the association of optic atrophy and contralateral papilloedema occurs has recently been examined and can not be attributed to a single explanation.[18] The hypotheses include (1) optic nerve compression together with raised intracranial pressure, (2) bilateral optic nerve compression, and (3) chronically raised intracranial pressure without direct optic nerve compression. In this case it is difficult to exclude compression of both optic nerves from the size of the tumour. However the bulk of the tumour was on the side of the optic atrophy and there was evidence of raised intracranial pressure both clinically and on CT scan. Thus a combination of 1 and 2 seems likely and is consistent with a diagnosis of true Foster-Kennedy syndrome.[12,24] Since it has now been established that the signs first described by Foster Kennedy cannot be used as 'an exact diagnostic sign' it has been suggested that this combination of clinical findings be termed the Foster-Kennedy sign. Sanders, in his study of six patients, concluded that fluorocein angiography should be performed on such cases in order to exclude local disorders at the optic disc.[25] However modern imaging techniques give a far more accurate analysis of the underlying pathology and are probably the investigations of choice in the Foster-Kennedy syndrome.

This case is of interest not only in its association with the Foster-Kennedy syndrome but also in light of the declining rate of visual loss as the presenting symptom in pituitary adenomas.[26,27] Although pituitary tumours are common, representing about 12% of intracranial tumours,[26] the Foster-Kennedy syndrome has not previously been described as an association. In older series loss of visual field was considered an early diagnostic sign in cases of pituitary tumours,[28] but more recent studies suggest that the incidence of visual abnormalities as a presenting feature is on the decline because of earlier diagnosis.[26,29] Hollenhorst reported a series of

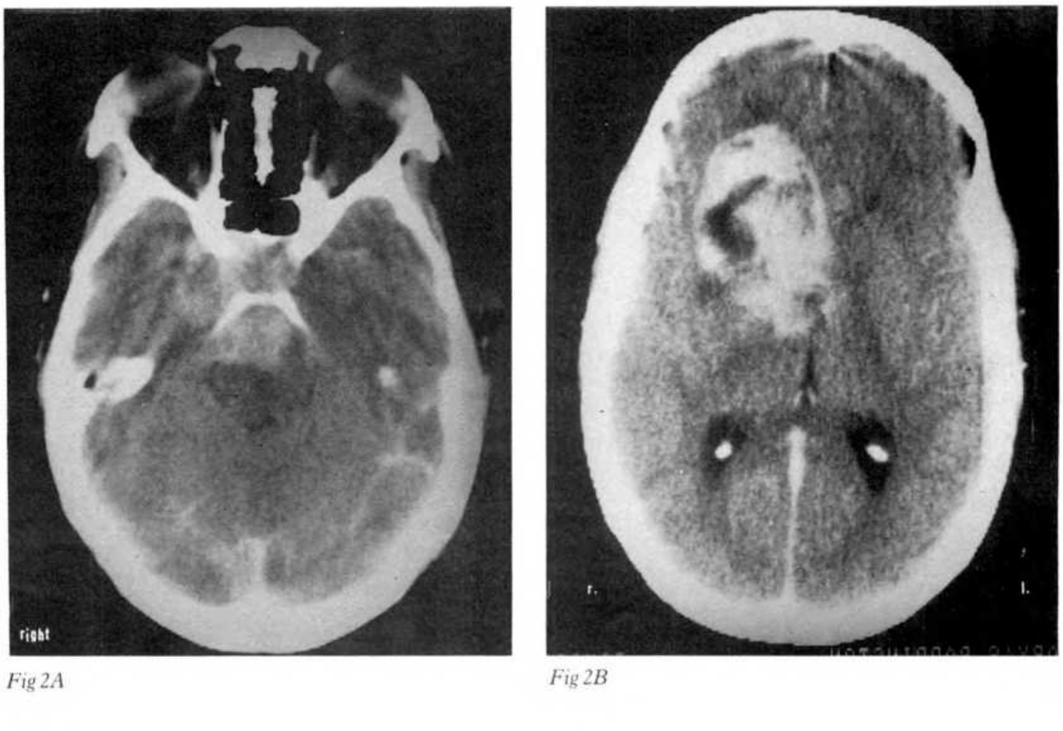

Figure 2 CT scan at presentation showing extent of tumour.

Fig 2A

Fig 2B

1000 patients of whom 70% had visual loss, 34% optic atrophy, and 6% extraocular muscle abnormalities.[30] However in Anderson's review of 200 patients[26] only 9% had visual field defects, 2% optic atrophy, and 1% extraocular muscle palsy. It is also of interest that the incidence of visual symptoms in prolactinomas was even lower, the non-secreting chromophobe adenomas having the highest incidence of visual symptoms at presentation.[26 28]

Although the incidence of patients with pituitary tumours presenting with visual symptoms is on the decline, ophthalmologists should still be wary of patients with such complaints especially when accompanied by other symptoms such as headache.

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Premalignant melanosis of the conjunctiva and the cornea in xeroderma pigmentosum

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Abstract

Xeroderma pigmentosum is a rare autosomal recessive dermatosis. The neoplastic changes in sunlight-exposed areas of the skin and eyes may be related to the impaired replication of ultraviolet radiation-damaged DNA. A 38-year-old Greek woman is reported with a mild form of xeroderma pigmentosum and primary acquired melanosis with atypia of her right limbal conjunctiva and cornea. The development of this precursor of conjunctival malignant melanoma in a xeroderma pigmentosum patient may support the putative role of sunlight exposure in malignant transformation of conjunctival melanocytes.

Xeroderma pigmentosum is an uncommon autosomal recessive actinic dermatosis which was first described in 1874 by Hebra and Kaposi.[1] This progressive disease of the skin and mucous membranes is characterised by abnormal sensitivity to sunlight, premature skin ageing, abnormalities of pigmentation, and multiple neoplasms.[2] Xeroderma pigmentosum frequently has ocular complications including photophobia, recurrent conjunctivitis, keratitis, keratoconus, lid abnormalities, and neoplasms.[2-8] A subset of xeroderma pigmentosum patients exhibit neurological deficits and mental deterioration.[8]

Xeroderma pigmentosum patients have a defect in the repair of DNA damage following exposure to ultraviolet radiation (UVR)[9] which is associated with homozygosity for one of at least seven different mutations.[10] Xeroderma pigmentosum has a global distribution and tends to occur in the offspring of consanguinous parents.

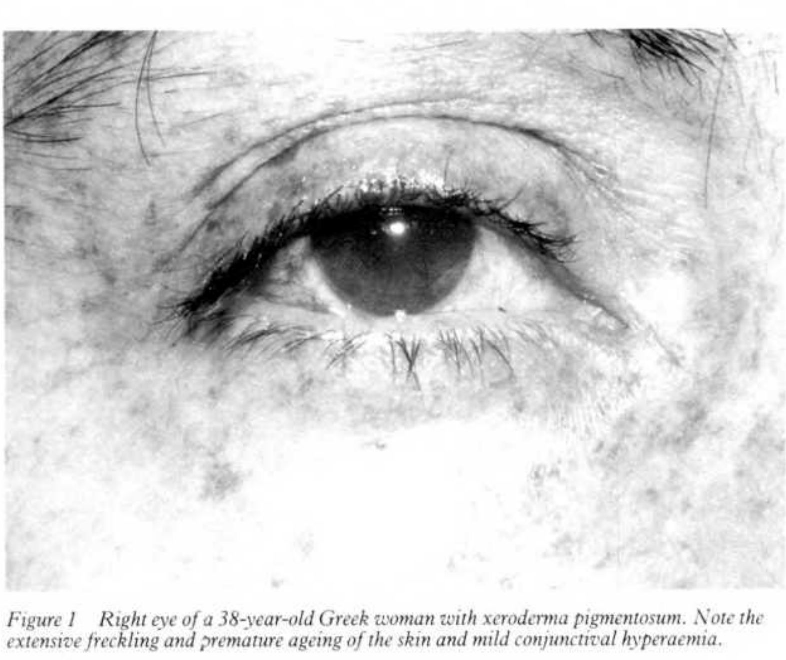

Figure 1 Right eye of a 38-year-old Greek woman with xeroderma pigmentosum. Note the extensive freckling and premature ageing of the skin and mild conjunctival hyperaemia.

Various types of ocular neoplasms in xeroderma pigmentosum patients have been reported. The most frequent tumour was squamous cell carcinoma followed by basal cell carcinoma.[8] There have been rare reports of malignant melanoma, involving the eyelids,[11] conjunctiva,[4 6 12] iris,[13] and posterior uvea.[14 15]

Primary acquired melanosis with atypia is an acquired precancerous unilateral condition of the conjunctiva[16] not arising as a result of long standing ocular inflammation, metabolic diseases, topical factors, or the patient's race. The melanocytes show atypical cytologic features including increased nuclear to cytoplasmic ratio upon microscopic examination.

We report a case of primary acquired melanosis with atypia affecting both conjunctiva and cornea of a 38-year-old Greek woman with xeroderma pigmentosum. The clinical and histopathological findings of this precursor of malignant melanoma, which to our knowledge has not been previously reported in xeroderma pigmentosum patients, are described.

Case report

In November 1987 a 38-year-old Greek woman with a mild form of xeroderma pigmentosum was referred by her ophthalmologist in Cyprus to the Oncology Department of Moorfields Eye Hospital. The patient had a history of a pigmented lesion of her right limbal conjunctiva which had been growing for 2 years. Her ocular history included recurrent conjunctivitis and photophobia since early childhood.

Two brothers and one sister expressed signs of xeroderma pigmentosum including skin abnormalities but no neurological deficit or mental deterioration. Two other sisters and a brother were clinically unaffected. The parents of the patient were not believed to be consanguinous. Her past medical history included appendicectomy and tonsillectomy.

On general examination widespread large freckles on the face (Fig 1), backs of the hands, arms, and neck were seen. The skin showed signs of loss of elasticity, telangiectasia, and atrophy. On the lower lip an erosive lesion with clinical characteristics of squamous carcinoma was noted.

The unaided visual acuity was 6/5 in the right, and 6/9 in left eye. Examination of the right eye showed a circumscribed flat pigmented conjunctival lesion extending round the temporal limbus (Fig 2) and exhibiting invasion into the superficial layers of the corneal epithelium (Fig 3). The corneal invasion extended to the temporal pupil margin. Increased vascularity was noted

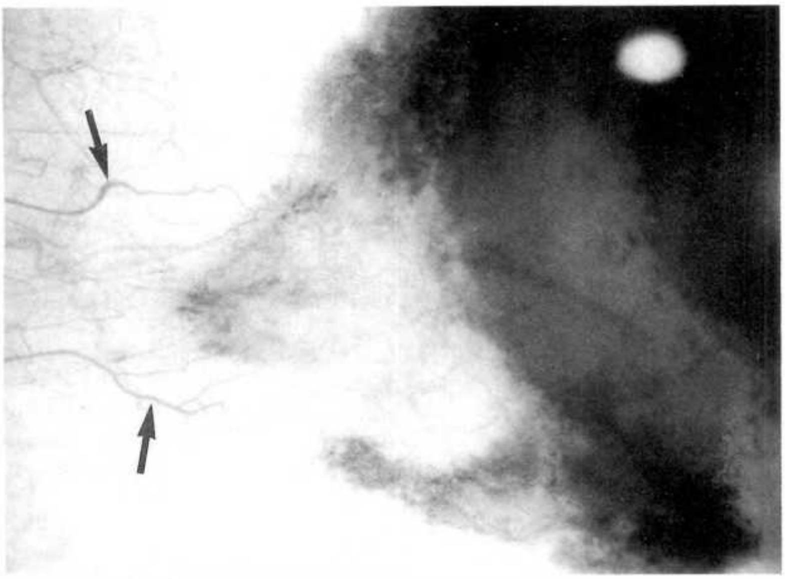

Figure 2 Detail of the right temporal limbus showing an area of flat conjunctival melanosis extending into the cornea. Note the feeder vessels (arrows).

round the limbal lesion which was not tethered to underlying sclera. The left eye and the remainder of the conjunctiva of the right eye were free from melanosis. In both eyes there was mild conjunctival hyperaemia and early development of pterygium.

The pigmented conjunctival lesion was resected en bloc with a lamella of underlying sclera and cornea. The affected corneal epithelium was removed using absolute alcohol. Triple freeze cryotherapy was subsequently applied to the limbal wound bed.

Histopathological examination of the corneal epithelium (Fig 4) showed an area of melanocytic proliferation maximal in the basal cell layer and with minor invasion of the more superficial epithelial layers. The biopsy of conjunctiva and limbus (Fig 5) showed much more widespread melanosis with in some areas considerable migration of atypical melanocytes into the epithelium. These findings were compatible with a diagnosis of primary acquired melanosis with atypia.

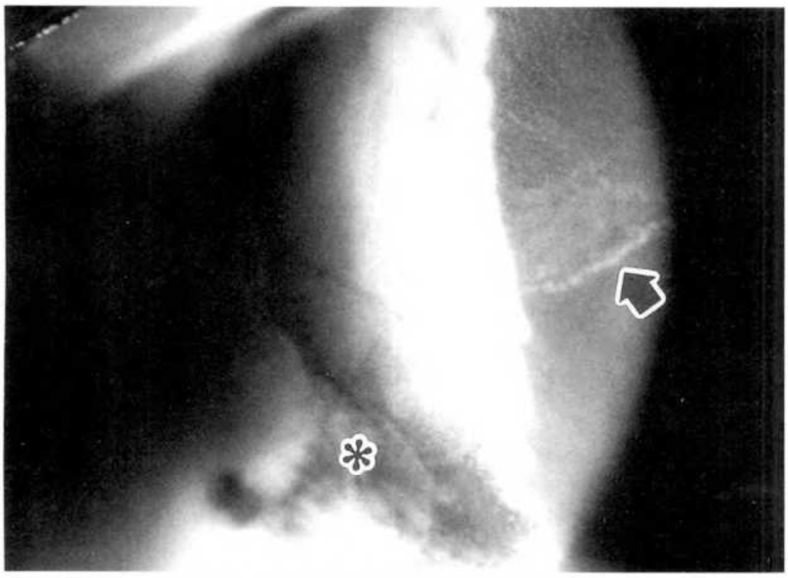

Figure 3 Lateral slit-lamp photograph of the right temporal limbus and cornea showing the corneal extension (arrow) of the conjunctival primary acquired melanosis (*).

In January 1988 1 month after treatment the conjunctiva had healed well and the cornea had re-epithelialised. In the meanwhile her lower lip lesion had been biopsied and histological examination confirmed the clinical diagnosis of squamous cell carcinoma.

When the patient was seen again in September 1988 the right eye including conjunctiva and cornea showed no signs of recurrence. For further ophthalmic follow-up she has been seen by her referring ophthalmologist in Greece from whom we have not heard since 1988.

Discussion

Several studies[9, 17, 18] have demonstrated an impaired replication of UVR damaged DNA in cells of xeroderma pigmentosum patients. This defect may be aetiologically linked to the various abnormalities in UVR exposed areas of these patients including atrophic and neoplastic changes.

In comparison with the general population xeroderma pigmentosum patients have an increased incidence of primary skin and ocular neoplasms such as basal and squamous cell carinomas and papillomas. The relative frequency and the biological nature of these tumours however are similar to those of normal individuals. Therefore xeroderma pigmentosum is used as a model for studying actinic carcinogenesis.

In an extensive review of 830 published cases of xeroderma pigmentosum by Kraemer *et al*[8] 97% of basal cell and squamous cell carcinomas and 65% of cutaneous malignant melanomas occurred on the face, head and neck, all sunlight exposed sites, compared with 80% and 20% respectively in the general US population. Ocular tissues that are exposed to ultraviolet radiation include the eyelids, the conjunctiva, the cornea, and the inferior iris. The ocular abnormalities including neoplasms in xeroderma pigmentosum patients are generally limited to these areas. These findings implicate a role of sunlight exposure in the aetiology of these tumours.

Conjunctival malignant melanoma has been rarely described in patients with xeroderma pigmentosum. In 1948 Saebo[1] reported a 17-year-old Caucasian woman with a recurrent pigmented corneolimbal tumour which was clinically diagnosed as 'melanomalignoma'. There had been a dark spot in the affected eye for several years before the onset of tumour growth. It is of interest that in this case the diagnosis of this neoplasm preceded the diagnosis of xeroderma pigmentosum. In 1962 Jensen[12] described a case of a limbal malignant melanoma arising from a pre-existing naevus occurring in 14-year-old Greenlander with xeroderma pigmentosum. In 1965 El-Hefnawi and Mortada[6] reported a 13-year-old Egyptian boy with a biopsy proven 'melanocarcinoma' of the limbus and a 14-year-old Egyptian girl with an advanced conjunctival melanoma with invasion of the whole orbit and the base of the skull. The authors did not comment on any possible precursor.

Although primary acquired melanosis with atypia might have been present in some of above

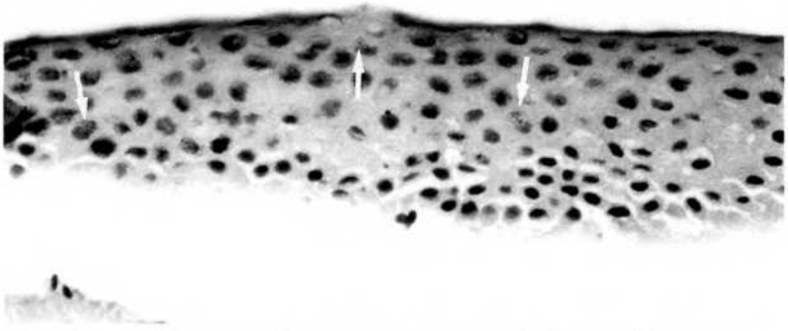

Figure 4 Histological examination of the affected corneal epithelium showed melanocytic proliferation involving both the basal cell layer and the more superficial epithelial layers. Note the presence of granular black pigment in the cytoplasm of the melanocytes (arrows).

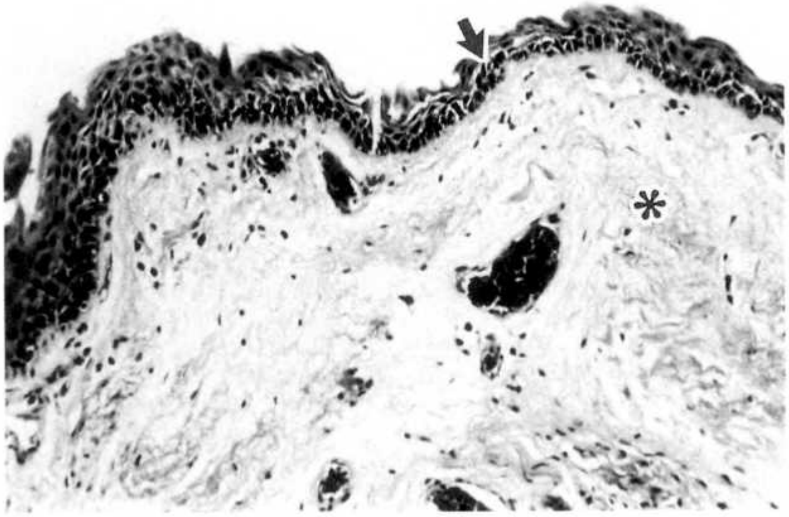

Figure 5 Examination of the biopsy of conjunctiva and limbus showed intraepithelial basilar nests of atypical melanocytes typical of primary acquired melanosis with atypia (arrow). Note the subepithelial elastotic degeneration (*).

cases the clinical and histological findings of such pre-malignancy complicating xeroderma pigmentosum have to our knowledge not been reported before. The conjunctival and corneal area of precancerous melanosis in the right eye of the 38-year-old Greek woman was treated to prevent further progression into frank malignant melanoma. It is interesting to note that all reported conjunctival melanocytic tumours including our case were located at the 9 o'clock or the 3 o'clock meridian of the limbus which are sites that are least protected from ultraviolet radiation.

The finding of four conjunctival malignant melanomas in a total of 830 published cases of xeroderma pigmentosum is suggestive of an increased frequency of this malignancy. Johnson *et al*[13] calculated that the finding of three patients with uveal melanoma in these 830 cases represents at least 23 times the expected number of cases. Henkind and Benjamin[19] estimated the frequency of conjunctival melanomas in comparison with uveal melanoma at 1:20–30. Thus the finding of four conjunctival melanomas represents approximately 750 times the expected number.

Ultraviolet radiation as a causative factor in malignant melanoma has been widely debated[20 21] but the finding of an increased frequency of conjunctival melanocytic (pre)malignancies in xeroderma pigmentosum patients strongly implicates a role of sunlight exposure in the malignant transformation of conjunctival melanocytes.

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Resection of intraocular squamous cell carcinoma

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Abstract

A patient with recurrent squamous cell carcinoma of the conjunctiva was referred with 20/20 vision in an eye with obvious intraocular extension. A modified iridocyclochoroidectomy was performed and the tumour was removed. Three and a half years later the patient's vision is 20/30 and there is no recurrence. This is the first case in which an eye has been successfully salvaged with documented intraocular squamous cell carcinoma of the conjunctiva.

Squamous cell carcinoma of the conjunctiva usually remains superficial, localised, and can be cured at that stage with resection and adjunctive cryotherapy or radiation.[1-4] Rarely the tumour invades either into the orbit or the globe. Approximately 60 cases of intraocular invasion have been reported.[5-19] Usually this complication occurs in patients with either neglected or recurrent tumours. In a 60 year retrospective review from the Mayo Clinic there were two of 22 cases of invasive squamous cell carcinoma of the conjunctiva invaded into the globe.[8] In a series of 104 epithelial tumours reported by Irvine, one had intraocular invasion; similarly one of 27 invasive carcinomas reported from the Wilmer Institute had intraocular penetration.[16 20]

Intraocular invasion from squamous cell carcinoma of the conjunctiva can have a number of clinical manifestations. We have noted it as an undiagnosed corneal perforation, anterior segment inflammation, a combined orbital and intraocular mass, a non-specific broad peripheral anterior synechiae, an apparently solitary intraocular mass, or a sheet of cells growing onto the iris surface,[1] other presentations have included a necrotising scleritis.[21] Nicholson and Herschler described a patient who presented with apparent anterior chamber inflammation in whom the correct diagnosis of squamous cell carcinoma was confirmed with aqueous paracentesis.[15]

The ocular prognosis for patients with intraocular invasion from conjunctival carcinoma has been dismal. All reported cases have required either enucleation or exenteration.[2-20] We report a patient with recurrent squamous cell carcinoma that invaded the globe in whom we were able to successfully salvage both the eye and vision.

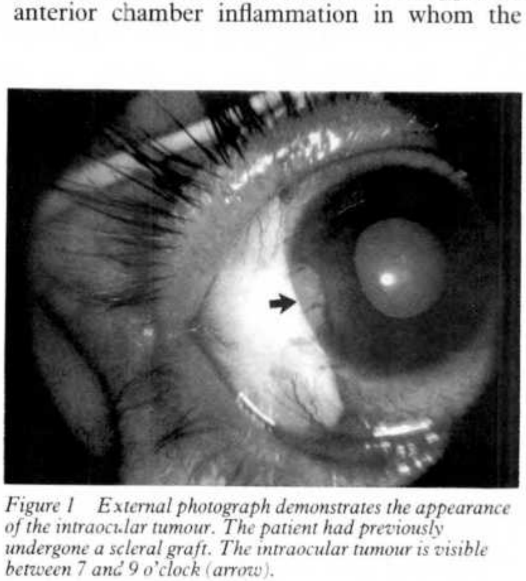

Figure 1 External photograph demonstrates the appearance of the intraocular tumour. The patient had previously undergone a scleral graft. The intraocular tumour is visible between 7 and 9 o'clock (arrow).

Case report

A 58-year-old female was referred with a recurrent right conjunctival squamous cell carcinoma with intraocular invasion. The patient was initially examined in January 1987 by her local ophthalmologist for an atypical area of solar damage at the right temporal limbus. In February 1987 this was resected and pathological examination revealed a squamous cell carcinoma. The tumour recurred 6 weeks later and a second resection was performed in April 1987. An en bloc excision of the tumour and the underlying 50% thickness sclera was performed. Adjunctive cryotherapy was delivered to the remaining scleral fibres and the edges of the resection. The area was closed primarily without a graft. The neoplasm recurred within 1 month in the same area and a third resection was performed in May 1987 with placement of a 10 mm diameter scleral allogeneic patch graft. Pathology sections demonstrated that all margins were clear.

Two months later in July 1987 intraocular invasion was noted (Fig 1) and the patient was referred to us for further management.

On our examination at that time the visual acuity was 20/20 in each eye. The left anterior segment and fundus were unremarkable except for areas of lattice degeneration without retinal breaks. The intraocular pressure was 14 mm Hg in the right eye and 16 mm Hg in the left.

In the right eye there was a large scleral graft at the temporal limbus. The cornea was clear. The iris and ciliary body were involved with an amelanotic mass from 7 to 9 o'clock. There was no pupillary distortion. There was trace flare without cell in the anterior chamber. Examination of the right fundus with both scleral depression and three mirror contact lens examination was unremarkable.

Ultrasonography demonstrated a mass involving the lens and ciliary body. The tumour was approximately 7 mm thick on standardised A scan.

Various therapeutic options were discussed with the patient and her family and it was decided to proceed with a scleral resection and a modified iridocyclectomy. The area around the scleral graft was explored and obvious tumour extension along both surface and under the graft

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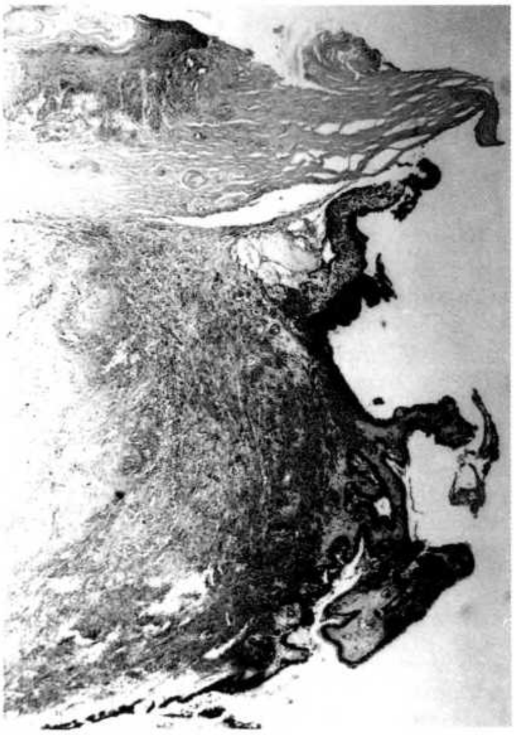

Figure 2A

Figure 2 (A) Low power photomicrograph of anterior portion of resected tissue (H and E, ×10). (B) Higher power photomicrograph showing invasive squamous cell carcinoma arising from the conjunctival surface. Note the hyperkeratosis and keratosis on the surface of the conjunctiva, and the invasion of a scleral canal (arrow) (H and E, ×40). (C) Higher power photomicrograph of the ciliary body invaded by squamous cell carcinoma, some of which has formed keratinising pearls (H and E, ×40).

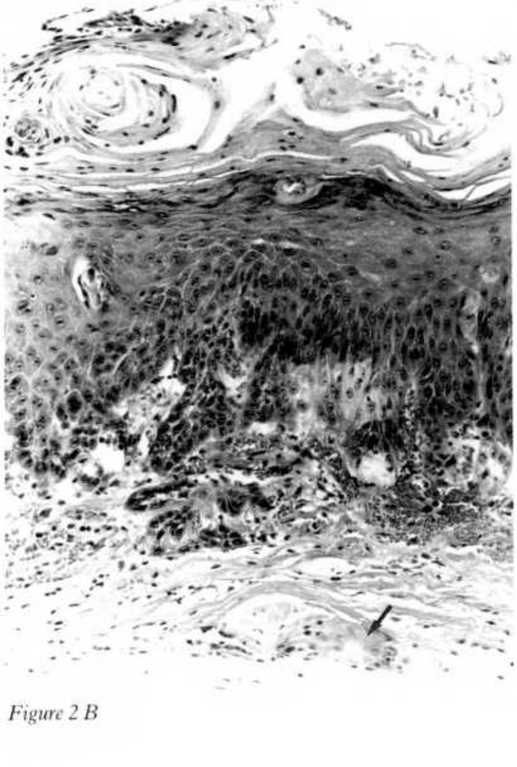

Figure 2 B

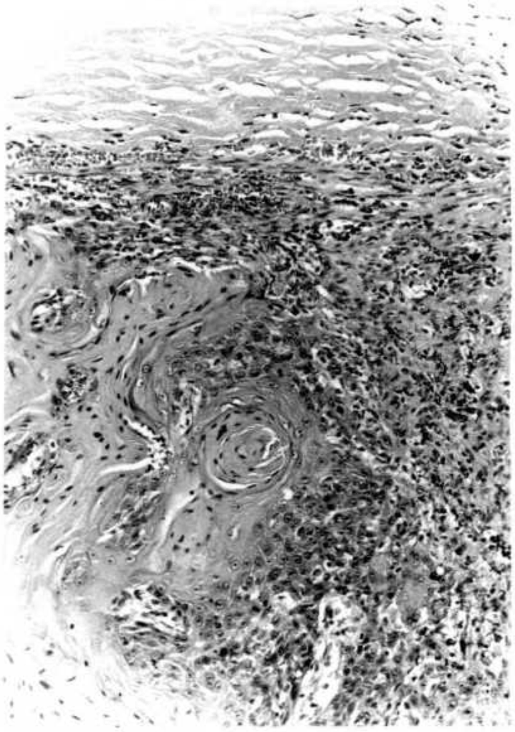

Figure 2C

was confirmed on frozen section. A large scleral resection approximately 17×12 mm in diameter was performed and the contiguous iris, ciliary body, and choroid were removed en bloc. Frozen sections of the margins were clear. A free allogeneic scleral graft was used to reconstruct the eye. Double freeze thaw adjunctive cryotherapy to adjacent sclera and conjunctiva was delivered in a standard manner. Microscopic examination of the resected tissue showed a keratinising squamous cell carcinoma arising from the conjunctiva and extending through scleral canals into the ciliary body (Figs 2 A, B, C).

Postoperatively the patient slowly developed increasing lens opacity over the next year. She subsequently had an extracapsular cataract extraction and the implantation of an intraocular lens by her referring ophthalmologist in August 1989. A YAG laser capsulotomy was performed and on her last visit in August 1990 her visual acuity was 20/30. There was no evidence of tumour recurrence and the pressure was 14 mm Hg.

Discussion

There are at least three important risk factors for intraocular extension of squamous cell carcinoma of the conjunctiva, neglected malignancy, recurrent tumours, and histologic tumour type.[7 9 10 16] Our case had repeat excisions with apparently clear margins but eventually developed intraocular penetration. The disparity between the apparently clear surgical margins and recurrence emphasises the limitations of standard frozen section control of tumour margins. While that histological technique is quite accurate to delineate horizontal tumour spread, especially with a small surgical specimen, its efficacy for sampling the deep surface is poor. We have had one other conjunctival tumour patient with clear frozen section margins who developed a recurrence because of inapparent tumour at the deep surgical line. These limitations with frozen section technique have led us to use adjunctive cryotherapy both to the base as well as the horizontal resection lines in all cases.[1]

Intraocular penetration and metastases from squamous cell carcinomas of the conjunctiva are rare.[1,8,16] In most series fewer then 2% of cases have intraocular penetration, and only two patients in the United States have had documented metastatic disease. In 10 patients reported from Saudi Arabia with advanced disease seven had intraocular invasion.[22] Mucoepidermoid and, possibly, spindle cell variants of squamous cell carcinoma are more locally aggressive and have a higher recurrence rate; each histological subtypes account for fewer than 5% of squamous cell carcinomas of the conjunctiva.[9,10,23]

Very few surgeons have attempted to salvage an eye with intraocular penetration of squamous cell carcinoma of the conjunctiva; all previous cases have required either enucleation or exenteration. Li and co-workers reported two patients who had modified en bloc resections; however both had positive margins and were enucleated within 1 day and 1 week of the initial surgery.[19] It is uncertain how many patients with intraocular proliferation of squamous cell carcinoma are candidates for a modified iridocyclochoroidectomy. We have examined five patients with intraocular extension from this tumour, and this was the only case in which we felt that this approach was indicated. Usually intraocular penetration by this malignancy is not amenable to local resection with ocular salvage because the tumour is too diffuse. Since 1903 a number of investigators have demonstrated that intraocular invasion is usually associated with diffuse spread in both the suprachoroidal space and the uvea.[18] Often the tumour is sufficiently friable to seed cells into the anterior chamber and simulate inflammation.[15] In some cases there is extensive orbital spread contiguous with the ocular involvement. In a minority of patients with apparently localised intraocular tumour a modified eyewall resection is a reasonable alternative.

This work was supported in part by NIH grant EYO 7504, and by unrestricted grants from That Man May See and Research to Prevent Blindness

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LETTERS TO THE EDITOR

Keratitis in Reiter's syndrome

SIR,—We describe a patient with Reiter's syndrome who presented with a bilateral anterior stromal keratitis with a ragged corneal epithelial defect in one eye. These findings are a characteristic but rare and poorly recognised complication of Reiter's syndrome.

Case report

A 28-year-old man presented with 1 week's history of redness, pain, and blurring of the vision of both eyes. One month previously the eyes had been red with a mucopurulent discharge but these symptoms had resolved spontaneously over a period of 7 days.

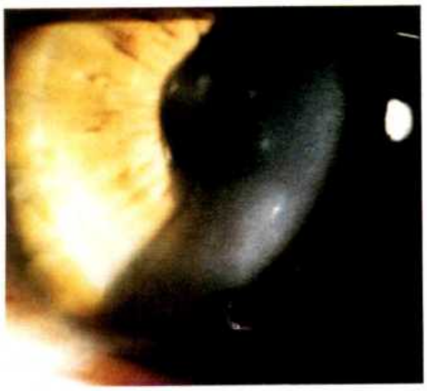

Figure 1 Anterior stromal infiltrates and punctate epithelial erosions in the patient's right eye.

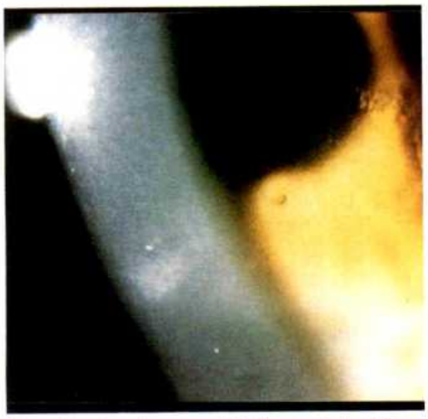

Figure 2 Anterior stromal infiltrates in the left eye.

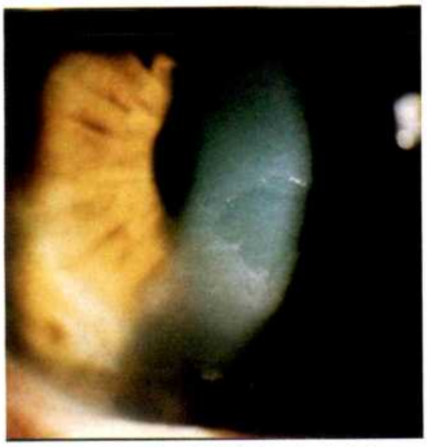

Figure 3 Ragged epithelial defect in the left eye.

Two months prior to the onset of his ocular symptoms he had had a diarrhoeal illness, followed shortly by polyarthralgia, and a diagnosis of Reiter's syndrome was made by a rheumatologist.

At the time of his initial ophthalmic examination he had coarse anterior stromal and epithelial infiltrates in both corneas (Figs 1 and 2), fine punctate erosions in the right eye, and a large, ragged epithelial defect in the left (Fig 3). He had fine conjunctival papillae in both eyes.

He was treated with guttae chloramphenicol 0·5% and guttae prednisolone 0·3% each four times daily. Within 1 month of presentation the keratitis had resolved completely without scarring.

Comment

Common ocular manifestations of Reiter's syndrome include conjunctivitis and iridocyclitis but, although it is mentioned by Duke-Elder,[1] keratitis is not well recognised as a complication by most ophthalmologists.

Keratitis, similar to that described here, was reported in 1972 by Mills and Kalina,[2] and more recently by Wiggins *et al*.[3] Lee and coworkers reported superficial punctate keratitis and pleomorphic anterior stromal infiltrates in 4% of patients with Reiter's syndrome in their study.[4]

Our case demonstrates all the clinical features of an established case of keratitis in Reiter's syndrome.

Anterior stromal keratitis, affecting mainly the peripheral cornea, and associated with ragged epithelial erosions, is a rare but characteristic finding in Reiter's syndrome. A prodromal conjunctivitis is usual as is spontaneous resolution.

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Statistical standards

SIR,—I was recently invited to give a talk to the Department of Ophthalmology in Oxford on statistical methods in eye research. I chose to structure my talk around a review of the standard of statistics in articles published in the *BJO* and I thought that your readers might be interested in my findings.

I reviewed all of the articles published in the *BJO* during the first 6 months of 1990 concentrating on their statistical content including design, presentation, analysis, and interpretation. I identified 42 articles that had employed a statistical analysis and a further seven where I thought that a statistical analysis would have been helpful but was not given. The methods used were typically very simple and often just consisted of tests such as the t test or χ^2 test.

Any assessment of quality is bound to contain a large subjective element but even allowing for this the standard was a little disappointing. I judged that 26 of the papers were either acceptable as they stood or needed only very minor changes perhaps of clarification. The remaining 23 contained what I would consider to be statistical errors. These errors ranged from the omission of important details to faulty design and the misuse of statistical tests. In very few cases were the errors so bad that the paper could not have been corrected, sometimes quite simply. However the errors do detract from the quality of the work and leave the reader in doubt about the conclusions.

These findings might at first sight seem surprisingly poor but they are very much in line with the results of similar reviews of published articles from journals covering other branches of medicine. The problem is well recognised and widespread, a solution is more difficult to find.

It is worth emphasising that the problem does not lie in the misuse of complex statistical techniques but rather in weak scientific method and a haziness about the underlying principles of statistical analysis. It is easy to point to poor medical education as the root of the problem, but medical students often do not see the need for courses in statistics and so pay comparatively little attention to them.

Perhaps it is up to the medical journals to take a lead by insisting on higher standards and by using referees who are trained in statistics.

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⁂ Many thanks to Dr Thompson for his interesting letter which contains much food for thought. It emphasises the gap which exists between clinicians and professional statisticians, a gap which it would be good to narrow even perhaps to the extent of rendering redundant some of the old well-worn jokes about statistics. One is aware however from many conversations with responsible and experienced clinicians that suspicion about statistics dies hard and there are still numerous ophthalmologists who believe that complicated statistics are sometimes used to attempt to prove theories which, if they were really true, would be obvious by commonsense alone.

From my point of view as editor I am, although suitably chastened, at least glad to see that we at the *BJO* are not alone in publishing some papers with statistics which do not satisfy the professionals try as we may to keep authors on the straight and narrow. Looking around at some of our sister publications I should not be surprised if some of them were even worse than us but unfortunately these figures are not vouchsafed to us in the current letter.

On a positive note: we should very much welcome an article from Dr Thompson on the subject of good statistical practice in ophthalmic papers. The last we published, admittedly on a restricted aspect of the subject, the confusion of 'eyes' versus 'patients' in ophthalmic statistics, was back in 1987.[1] – ED, *BJO*.

1 Newcombe RG, Duff GR. Eyes or patients? Traps for the unwary in the statistical analysis of ophthalmological studies. *Br J Ophthalmol* 1987; **71:** 645–6.

Amblyopia

SIR,—I congratulate Drs Lithander and Sjöstrand on their excellent study of amblyopia and the results of treatment.

Having been involved with the treatment of amblyopia for more than 30 years my views have altered very little.

My work reported in 1964 still stands that a monitored period of total occlusion overcomes amblyopia quickest and best. As improvement occurs one can modify the techniques to part time, or partial, to achieve the final result.

However in the past 10 years or more I found the best answer was prevention of amblyopia and this was achieved by early peripatetic orthoptic screening in postnatal, infant, and preschool clinics.

This meant that squints and amblyopia were detected very early and, with prompt referral, required less specialist treatment; and amblyopia was only relative in depth and required only minimal occlusion to obtain a cure. Indeed most children were detected before amblyopia (as defined) had had time to occur.

I would urge the need to continue to strive for early screening and public education before the age of 4 years contrary to the Hall report.

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Cataract surgery

SIR,—The problem of the enormous backlog of cataract surgery in the third world will not I fear be solved by the methods advocated by Mr Arthur Steele.[1]

I was fortunate to get my surgical training in Pakistan where my colleagues routinely did 150 cataract operations single-handedly in a 6 h session. Their technique was a Graefe knife incision, peripheral iridectomy, intracapsular lens extraction with forceps, or cryosurgery and one to three corneoscleral sutures with 8/0 silk. The surgery was of superb quality and the results were excellent.

If we had performed the surgery with microscopes, three-stage incisions, IOLs, running 10/0 sutures, etc, then I suspect the rate would have fallen from 20–30 operations an hour to two to three an hour. The resulting cost would be so high that only the wealthy could afford treatment.

No-one would try to ignore the brilliant advances in ophthalmic surgery developed in the west. However I would urge my colleagues there to accept that for huge numbers of cataract blind in Africa and Asia such techniques may not be the most appropriate and that simple methods in expert hands can give excellent results at low cost.

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1 Steele A. Cataract surgery. (Editorial.) *Br J Ophthalmol* 1990; 74: 130–1.

Dominant cone dystrophy starting with blue cone involvement

SIR,—The authors of the paper[1] in vain looked for a blue gene defect. The blue-yellow colour vision defect they observed however finds its origin in the physiology of the retina. Pathology of the macular region, if fixation is preserved, gives rise to blue-yellow defectiveness regardless of the cause: X-linked or dominant inherited cone dystrophy, pigmentary dystrophy, intoxication by synthetocal antimalarial agents, and so on.[2]

Cone dystrophies start either foveolar or perifoveolar. The latter type is known as peripheral cone dysfunction and is characterised by a disturbed full field cone ERG, a relatively well preserved visual acuity and normal colour vision or an acquired type III blue-yellow colour vision defect.[3,4] Static perimetry reveals a perifoveolar dip.[2] The blue-yellow defect, often dichromatic, is an exaggerated small field tritanopia. Case VI.6 is a good illustration. This patient could not read the 8° plate tests but made a classic tritan response with the 2° Panel D-15 test.

The dystrophic process affects the perifoveolar cones, including the blue cones which have their maximum density at 1·5° eccentricity. The blue cone-free foveolar region becomes enlarged resulting in a strong decrease in blue sensitivity.

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Reply

SIR,—In an effort to be concise we have apparently not been sufficiently clear. The main conclusion of our article – concerning a progressive cone dystrophy and not a cone dysfunction – was that our family represents a distinct, as yet undescribed entity (last sentence of the abstract and last sentence of the last paragraph but one of the discussion).

It is now sufficiently well documented that genes coding for visual pigments may if subject to mutation, lead to ocular disease: X-linked cone dystrophy in the case of a deletion of the red cone pigment gene,[1] autosomal dominant retinitis pigmentosa in the case of a mutation of the rhodopsin gene.[2,3] Sufficient reason for us to ask for an analysis of the tritan gene (thus not as Dr Pinckers states: 'The authors . . . looked in vain . . .).

L N WENT
M J VAN SCHOONEVELD
J A OOSTERHUIS

1 Reichel E, Bruce AM, Sandberg MA, Berson EL. An electroretinographic and molecular genetic study of X-linked cone degeneration *Am J Ophthalmol* 1989; 108: 540–7.
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3 Drya TP, McGee TL, Hahn LB, *et al* Mutations with the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa *N Engl J Med* 1990; 323: 1302–7

Cause of blindness in the Central African Republic

SIR,—It was with much interest I read the recent paper by Dr Andrew Potter.[1]

One of the important early steps in the development of a national prevention of blindness programme is the assessment of the dimensions of the problem of blindness and a characterisation of the leading causes of blindness in a particular country or region. The findings in the Central African Republic show that cataract and uncorrected aphakia accounted for more than half the blindness, a finding in common with many countries.

Quite rightly Dr Potter suggests that one solution to the problem of cataract blindness would be to train eye workers to perform intracapsular cataract extractions (ICCE). One argument made in support of the more expensive operation of extracapsular cataract extraction (ECCE) with intraocular lens implantation has been the permanence of the correction of the surgically-induced aphakia. The aphakic glasses used after intracapsular extraction can become broken or lost and frequently are not replaced.

Few data are available on the proportion of people who have had intracapsular surgery and who continue to wear their corrective glasses I was wondering whether Dr Potter had information on the proportion of people who were blind because of uncorrected surgical aphakia, and also the proportion of aphakics who in fact remain blind after surgery either because of surgical complications or loss of their aphakic glasses.

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1 Potter A. Causes of blindness and visual handicap in the Central African Republic. *Br J Ophthalmol* 1991; 75: 326–8.

Reply

SIR,—Those of us working in Africa are well aware of the problem of uncorrected aphakia. There are a number of reasons for this problem. Spectacles may not have been provided at the time of the original cataract extraction. Patients may not have found the money for their purchase. The glasses may well have been broken or lost at a later date. Other patients are unable to make the effort to adapt to the larger image and visual distortions. Still others were given a prescription for a pair of glasses which when they presented it to a private optician found the cost prohibitive. A depressing litany of excuses that I regularly encounter.

From my 4 years' work in the Central African Republic I found that uncorrected aphakia accounted for 8% of bilateral blindness. This included a majority who had one eye blind from unoperated cataract and the other aphakic eye without spectacle correction. Of 26 patients with bilateral aphakia without spectacle correction eight had other problems that could not be improved with glasses (optic atrophy, maculopathy, pupillary membrane, retinal detachment, and phthisis.)

Now the alluring prospect of extracapsular cataract extraction (ECCE) with intraocular lens implant is suggested for Africa. This could solve the problem of uncorrected surgical aphakia. But is it realistic for rural Africa at the present time?

ECCE is a more complex surgical procedure requiring sophisticated equipment (needing maintenance) and a longer training for the surgeon involved who would have to be a fully trained medical doctor. Intraocular lenses are more expensive than aphakic spectacles. In the Central African Republic there is only one permanent centre for cataract surgery. It is in the capital Bangui. The whole of the rest of the country and the majority of the population are very infrequently served by visiting surgeons who may spend up to a week in any one place. Such provincial hospitals and dispensaries may well not have mains electricity.

The patients who attend for surgery are elderly and poor. Some may have travelled for two or three days from their homes on foot.

Each has to be accompanied by a sighted relative who must feed, wash, and accompany them to the toilet. The maximum time that they will tolerate being absent from home is about 10 to 12 days. Follow-up after discharge is virtually impossible for the surgeon will no longer be available and the patients cannot be expected to attend for so little assumed benefit.

All this must be taken into consideration before contemplating a change from ICCE to ECCE.

It is also true (even though it may depress us) that what many elderly illiterate patients, and the families on whom they depend, want from their surgery is restoration of functional sight so that even though an aphakic patient without spectacle correction is technically blind (visual acuity below 3/60) the patient is at least able to navigate unaided around the homestead. The change from PLP to counting fingers at 1 metre may be adequate for this.

What really would benefit hundreds of thousands of cataract-blind people in Africa would be more surgeons willing to dedicate themselves to serving in rural areas. This would be many times more useful than investing in technology.

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BOOK REVIEWS

Perspectives in Glaucoma: Transactions of First Scientific Meeting of The American Glaucoma Society. Eds M Bruce Shields, Irvin P Pollack, Allan E Kolker. Pp 290. £51.60. John Wiley: Chichester, West Sussex. 1988.

This volume records the transactions of the inaugural meeting of the American Glaucoma Society. In the preface the editors explain its triple aims: to allow the views of the society on glaucoma management to reach a wide audience; to document the founding of the society, and to honour the memory of the late Dr Charles Phelps, one of the society's founder members. The book succeeds in all these aims.

The distinguished authors and representatives of the society in the first 12 chapters provide a highly readable, scholarly, and entertaining account of some of the latest and most exciting developments that have taken place in the understanding and hence the rational management of glaucoma in recent years. Drance gives an excellent review article on the role of intraocular pressure in the development of glaucomatous damage of the optic disc. Hayreh reviews the relationship between glaucoma and ocular vascular disease, and Quigley gives an informative and helpful chapter on the clinical examination of the nerve fibre layer. Many of the authors in this book pay tribute to the contributions of Dr Phelps to glaucoma research, and chapter 3 is devoted entirely to his research interests and achievements. This chapter is written by Mansour Armaly and leaves the reader in no doubt as to the tremendous contribution to the understanding of glaucoma made by Phelps; it also shows in what high regard he was held by all who knew him.

Chapters 5 to 12 concentrate more on recent research efforts and the development of new modes of treatment. Like the first four chapters they are well written, brief enough to keep the reader's attention, and contain a wealth of references that will be of use to anyone undertaking research in these fields.

Section V is concerned with current concepts in filtering surgery, and this was the least satisfactory section of this book The critical appraisal and scientific approach which so exemplify the first half of the book give way to more of a 'personal experience' approach. This may reflect the authors' desire to pass on their surgical views to a readership less surgically orientated than most ophthalmologists practising in the UK. Some rather sweeping statements and generalisations appear unsupported by references. It was surprising to read that up to 14% of trabeculectomies performed in the USA require a choroidal tap for shallow/flat anterior chambers, as drainage of choroidal effusions after trabeculectomy must be one of the rarest of surgical procedures in the UK It was disappointing, though perhaps inevitable owing to the three years that have passed since the meeting was held, that the success of 5FU could not yet be confirmed. Its role in repeat filtering surgery is now well established. Moreover, a chapter on the successful use of single plate Molteno tubes appears, yet present knowledge now favours the use of the two-plate Molteno tube because of greater efficacy. There was also no mention of the use of expandable intraocular gases, which have proved very useful for reforming flat anterior chambers after drainage surgery.

Section VI entitled 'Advances in management of glaucoma,' covers some recent aspects of glaucoma research, and topics such as YAG laser trabeculoplasty and the use of P-aminoclonidine to prevent post-laser pressure spikes are included. There is an excellent chapter by Elliot Werner on the difficulties involved in determining whether visual field loss has progressed between successive examinations. This is an important chapter which should become a required reference for papers claiming success or otherwise of a particular glaucoma treatment. However, the chapter on a new treatment for thrombotic glaucoma is not in keeping with the standards set in the rest of the book. It relates the authors' experience of a new method of laser iridotomy in the treatment of thrombotic glaucoma carried out on four eyes, one of which was normotensive and one had a vision of only light perception. It describes the pretreatment IOP as 39 mm Hg, and then makes the incomprehensible statement that 'this was adequate in two of the four eyes.'

In conclusion, this book is successful and instructive and provides a suitable commemoration of the inaugural meeting of the American Glaucoma Society as well as a glowing tribute to the memory of Charles Phelps. It will be of particular interest to ophthalmologists concerned with the management of glaucoma patients and to those with a research interest in glaucoma

PETER K WISHART

Eye Diseases in Hot Climates. 2nd Edn. By John Sandford-Smith. Pp 242. £12.00. Butterworth: London, 1990.

The second edition of Mr Sandford-Smith's excellent book on eye diseases in hot climates is written primarily for the general medical officer, ophthalmic assistant, or ophthalmic nurse working in areas of the world with limited eye care services. After dealing briefly with the basic sciences and examination of the eye the author systematically describes the important eye conditions seen in developing countries in the context of their diagnosis and management.

Trachoma, onchocerciasis, xerophthalmia, and leprosy are all dealt with in detail, including the most recent information on the simplified classification for trachoma, the relationship between vitamin A deficiency and child mortality, the introduction of ivermectin for the control of onchocerciasis and the use of multiple drug treatment in the management of leprosy. All these sections will be of interest not only to the non-ophthalmologist working in developing countries but also to the expatriate ophthalmologist whose previous clinical experience with these blinding diseases is likely to be minimal

The text is written in a simple and easily readable style and is excellently illustrated with line diagrams and colour plates. This book is essential reading for all doctors and paramedical workers involved in delivering eye care in developing countries of the world.

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NOTE

Ophthalmology in Developing Countries

A symposium on Ophthalmology in Developing Countries will be held on 12–13 March 1991 under the auspices of the Francis I Proctor Foundation for Research in Ophthalmology of the University of California School of Medicine at San Francisco, California, USA. Details from Extended Programs in Medical Education, Room LS-105, University of California, San Francisco, California 94143–0742, USA.

Correction

We regret that in the November 1991 issue of the British Journal of Ophthalmology two figures were transposed. Figs 1A and 1B on page 685 (paper by Spaide *et al*) should be Figs 1A and 1B on page 698 (paper by Erny *et al*) and Figs 1A and 1B on page 698 should be Figs 1A and 1B on page 685 The legends are correct as they stand. Loose leaf copies of both corrected papers are provided in this issue

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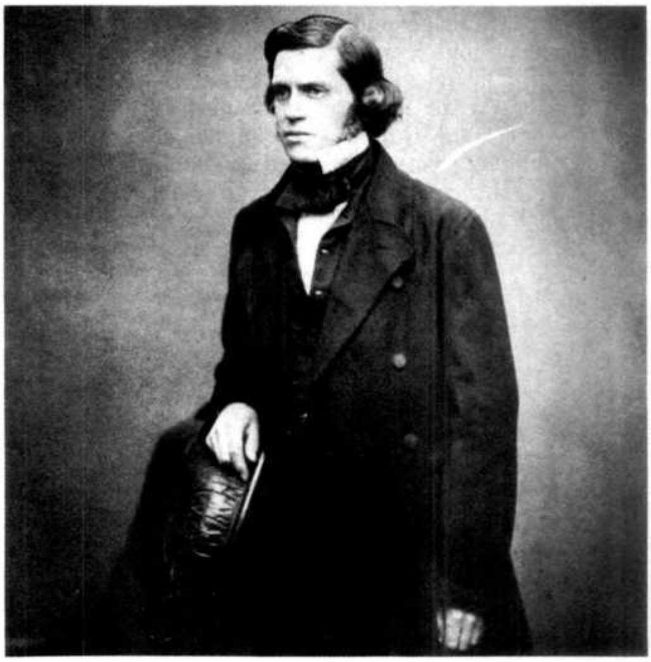
BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

Sir William Bowman – 1816–1892

Sir William Bowman, 'the founder of British ophthalmology,' died on 29 March, 1892. Centenaries are admirable incentives to reflect on our famous forebears, to pay them homage, to allow our current struggles to recede into the perspective of time, and to let us indulge in a little humility while glowing in the awareness that we are all leaves on that ever-expanding tree of knowledge which was planted in the wasteland, somewhere to the east of Eden.

William was the third son of a Cheshire banker cum naturalist; he was fortunate to have been born in the year after Waterloo, when the uncertainties and travails of the long war could be forgotten; England was confident, powerful and buoyant, with pent-up energies, which erupted in every sphere. In young William's case the early desire to experiment led to a gunpowder explosion, which called for treatment by Joseph Hodgson (later president of the Royal College of Surgeons and founder of the Birmingham Eye Hospital). William was so inspired by this encounter that, at the age of 16, he enlisted as Hodgson's apprentice.



Photograph kindly supplied by Moorfields Eye Hospital.

After working in Birmingham, he graduated to London, as demonstrator in anatomy, at King's College, taking advantage of a new microscope (the reward for his exact calibration of the cardiac orifices) to unravel the intricacies of human histology. These had to be gleaned from teased-out tissues, as seen by reflected light, since stained sections were not yet available. Thence followed a stream of publications, which also led him to a fellowship of the Royal Society at the age of 25, and of the Royal College of Surgeons three years later, and which have left his name as the label for various micro-anatomical structures and surgical instruments.

By the age of 30 he was elected to the staff of Moorfields, as one of the first British surgeons to devote his life to ophthalmology, and the first in England to make use of the ophthalmoscope which had been invented in 1847 by Charles Babbage (the bicentenary of whose birth also falls this year); albeit this device was largely neglected until taken up by Helmholz in 1851. It was during this year that he met, at the Great Exhibition in London, Von Graefe and Donders, who remained his close friends for the rest of their lives. Indeed, he was the first in England to perform the iridectomy for glaucoma, which Graefe had just proposed. Soon afterwards Florence Nightingale became his collaborator and lifelong correspondent, and he was able to keep her supplied with trained nurses during the Crimean Campaign.

In 1880, as the established authority in England, he founded the Ophthalmological Society of the United Kingdom, the rebus of his name appropriately crowning the coat-of-arms that was later granted to the Society, and thence to its successor, the College of Ophthalmologists, in the form of a symbolic archer. Each year his prowess is recalled in the tributes of successive speakers in the annual lectures that bear his name.

His life appears to have been unblemished, and sustained by a devout Christian assurance, which was shared by his large, supportive family, as were his wider interests in nature and in art. He was modest and abstemious, gentle and thoughtful in manner, quickly seizing the salient points of every case, yet very reserved, giving his opinion in a few decisive words; and he was meticulous in the work to which his life was dedicated. No clouds or disputes seem to have troubled his last years. He died in his home, near Dorking, and was buried in the neighbouring church of Holmbury St Mary, honoured by the whole world of ophthalmology, and an example to us all.

The details of his life and achievements are recorded in the *Dictionary of National Biography*, Supp 1, and were well described by Frank Law in the *Survey of Ophthalmology* (1975; **19:** 302). Two engaging memoirs can also be found in Norman Ashton's Bowman Lecture, and his Presidential Address to the Society (*Trans Ophthalmol Soc UK* 1965; **85:** 199 and 1980; **100:** 1), with echoes of his boyhood, and reproductions of the elegant micro-anatomical sketches which Ashton had unearthed from the Moorfields records.

PATRICK TREVOR-ROPER

Editorial

The ‘detached’ rectus muscle

Locating and repairing a lost or slipped rectus muscle can be challenging and is by no means always successful. It is perhaps not surprising that figures on the incidence of this complication are hard to come by, but it is certain that every ophthalmologist is likely to have to deal with it at some stage during his or her career.

The initial diagnosis may be difficult if the patient is in the early postoperative phase or if the eye has suffered recent trauma. Weakness may not be profound if a detached muscle retains some function through the muscle sheath or adjacent Tenon's capsule; indeed, many eyes have greater than 10° of ductions beyond the midline in the direction of action of the detached muscle. Clinically a detached muscle should be suspected if there are reduced ductions associated with widening of the palpebral aperture and exophthalmos in the direction of gaze of the affected muscle. Saccadic velocity and active force of the muscle are also reduced.

A detached rectus muscle falls into one of two categories. The slipped muscle is one which has been surgically disinserted and reattached to the sclera but has retracted within its Tenon's capsule which itself remains attached to the sclera; 90% of these can be successfully reattached.[1] The lost muscle has lost all attachments to the globe; in Plager and Parks series[2] only one out of 10 lost medial rectus muscles was found at surgery. The vertical recti and the lateral rectus retain attachments to the oblique muscles via the intermuscular septum and these muscles may be located by first finding the nearby oblique muscle and pursuing its attachments. The medial rectus, however, has no such attachments and may thus more easily recoil through the posterior Tenon's capsule into the orbital fat; blind searching for a lost muscle can lead to laceration of the posterior Tenon's capsule and subsequent adherence syndrome due to the prolapse of intraconal fat.

Computed tomographic scanning can help to localise the lost muscle preoperatively and, if surgery is carried out without atropine premedication, the oculocardiac reflex is a useful indication that a piece of tissue is harbouring the lost muscle. Some authors recommend the use of the operating microscope for identifying the sleeve of Tenon's capsule down which the muscle has vanished.

The timing of surgery is a compromise between allowing recovery of the muscle which has been traumatised or has undergone surgery but not allowing enough time for contracture of the antagonist muscle to occur. If surgery is delayed then this muscle will certainly need to be recessed and then any subsequent transposition surgery must be deferred to allow the anterior segment vasculature time to recover.

Careful removal of the anterior Tenon's capsule overlying the muscle tendon and the use of full thickness locking suture bites can help to minimise the incidence of slipped muscle. Cleaning of the muscle posteriorly is not necessary and the preservation of the intramuscular septum assists in the tracing of a subsequent lost muscle.

In this issue MacEwan, Lee and Fells present a paper which discusses the aetiology and management of the detached rectus muscle. The authors present their personal experience of 17 cases. They propose a new and useful classification of lost muscle which is based upon the mechanism of loss. Arguments are put forward for early exploration of a lost or slipped muscle and also for the timing and execution of effective transposition surgery which avoids anterior segment ischaemia.

R HARRAD

1 Plager DA, Parks MM Recognition and repair of the slipped rectus muscle *J Paediatr Ophthalmol Strabismus* 1988, 25: 207–74.

2 Plager DA, Parks MM Recognition and repair of the ‘lost’ rectus muscle A report of 25 cases. *Ophthalmology* 1990, 97: 131–7

British Journal of Ophthalmology, 1992, 76, 131–136

ORIGINAL ARTICLES

Aetiology and management of the 'detached' rectus muscle

Caroline J MacEwen, John P Lee, Peter Fells

Abstract

The clinical features and management of 17 cases of detached extraocular muscles are described. They are classified into four groups: (1) the muscle which is cut and lost during squint surgery, (2) the muscle which breaks during squint surgery, (3) the muscle which slips following squint surgery, and (4) the muscle which is damaged during facial or orbital trauma. The prognosis for group 1 is poor whereas groups 2–4 have a good chance of successful muscle relocation.

One of the most serious complications of squint surgery is loss of one of the rectus muscles. This may occur either during the surgical procedure itself or in the immediate postoperative period when the muscle slips from its new (recessed or resected) insertion.[1][2] In addition, extraocular muscles may become traumatically detached from the globe when they rupture or are transected as the result of any injury or during the course of retinal detachment, orbital, or strabismus surgery.[3][4]

In this paper we, firstly, report our experience of 17 cases in which one of the rectus muscles became detached from the globe; secondly, classify the different types of muscle loss; and thirdly, discuss the clinical features, management, and prognosis of such cases.

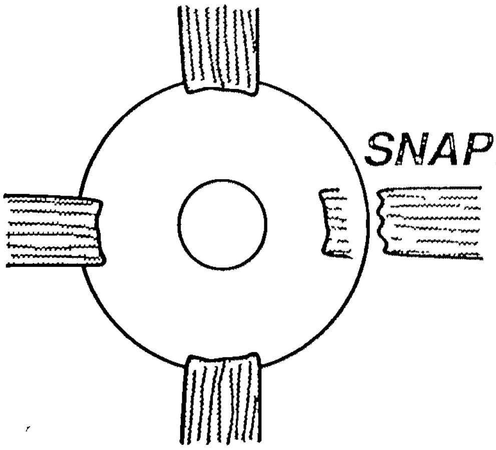


Figure 2 The muscle which snaps leaves a small tuft of insertion attached to the eye.

Patients and methods

The patients included in this series are all those who presented to or were referred to any of the authors with a detached rectus muscle. These patients were referred either at the time of surgery, postoperatively, or in the period following injury.

Patients belonged to one of the following four groups.

GROUP 1

Cases in which the muscle was inadvertently cut free from the globe and lost during squint surgery (Fig 1). In each instance the muscle had become completely detached from the globe and free from any suture attachments during the course of an otherwise uncomplicated resection/

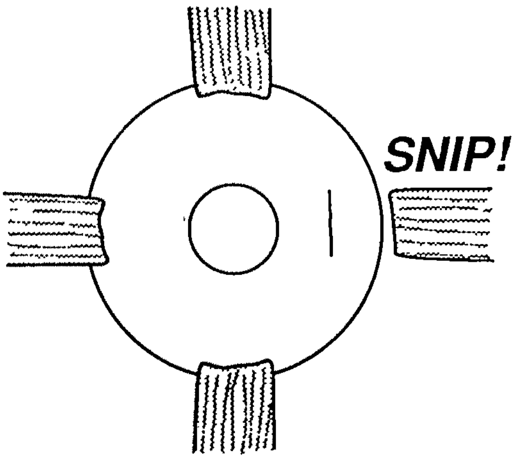


Figure 1 The muscle which is lost during surgery is completely detached from the eye.

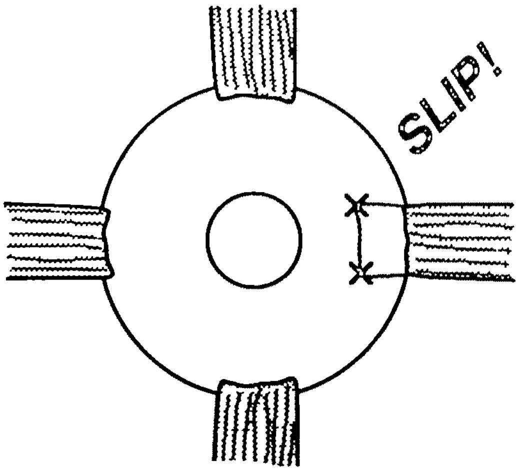


Figure 3 The slipped muscle contracts within its capsule remaining in contact with the eye via this attachment.

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Accepted for publication 26 July 1991

recession procedure. These muscles could not be re-located by the referring surgeon.

GROUP 2

Cases in which one of the muscles traumatically snapped during the course of squint surgery (Fig 2). The muscle was not surgically cut from the globe but broke while being held on the squint hook. In some cases the affected muscle had been damaged by previous surgery, trauma, or disease.

GROUP 3

Cases in which the muscle 'slipped' in the early postoperative period (Fig 3). In all cases the involved muscle appeared to be securely attached to the globe at the end of the initial squint operation. However immediately postoperatively it became apparent that one of the extraocular muscles had slipped from its position; in all cases the clinical impression of a slipped muscle was confirmed at re-operation.

The characteristic features of this type of muscle loss are: an initially satisfactory surgical result which over a few hours develops a marked squint with incomitance. Diagnostic criteria included large over or under correction, limited eye movement in one direction, and widening of the palpebral fissure in the field of limited duction.

GROUP 4

Cases of facial or orbital injury. In this group the muscle was damaged during facial trauma and became detached from the eye because of blunt or penetrating trauma.

Results

PEROPERATIVE MUSCLE LOSS (GROUP 1)

There were four patients with peroperative loss of a muscle. In two cases (cases 1 and 2) the muscle was relocated at the time of initial surgery and in two (cases 3 and 4) the muscle was not found until at least one re-exploration had been performed (Table 1). In all instances the lost muscle was the medial rectus. Three cases were undergoing a resection procedure for exotropia and the remaining one a recession for esotropia. In all cases the muscles had been cut from the globe as part of the surgical procedure and during the course of this the sutures had either been cut out or become disinserted from the muscle allowing it to retract into the orbit.

Table 1 Peroperative muscle loss

Case	*Surgery*	*Muscle*	*Surgery*	*Outcome*
1	MR+ LR−	MR	3 surgeons – found muscle	Good
2	MR+ LR−	MR	2 surgeons – found muscle	Good
3	MR− LR+	MR	Unable to relocate muscle Re-exploration 1 not found. Re-exploration 2 found	Good
4	MR+ LR−	MR	Unable to relocate muscle Transposition nasal slips of IR and SR	45 D exo AHP No adduct

Finally full nasal transposition with 5 mm resection of the IR and SR – good result.

MR=medial rectus; LR=lateral rectus, IR=inferior rectus, SR=superior rectus, +=resected, −=recessed, AHP=abnormal head posture, D=prism dioptre exo=exotropia.

In both cases that were relocated at the time of the initial surgery, one of the authors was present in the operating theatre and was able to relocate the missing muscle. It was found to be extremely useful to have the assistance of the surgeon who had lost the muscle. His knowledge of the circumstances leading up to the loss provided valuable information enabling the muscle to be relocated.

The other cases were referred postoperatively following failure to relocate the affected muscle. In case 3 the medial rectus fell off the muscle hook during a marginal myotomy. It was not relocated at the first exploration but computed tomography (CT) scans demonstrated that it remained attached to the globe (Fig 4) and was relocated at the second re-exploration.

In case 4 when the medial rectus was not found the nasal halves of the inferior and superior rectus muscles had been transposed to the anatomical insertion of the medial rectus muscle in an attempt to obtain some postoperative adducting force. However when the patient was referred she had a 45 dioptre exotropia with no adduction (Fig 5) and was attempting to maintain binocular vision with a marked abnormal head posture (Fig 6). In addition the medial conjunctiva was severely scarred and heaped up (Figs 5 and 6) because of extensive dissection while attempting to relocate the missing muscle. CT indicated that the medial rectus had retracted into the orbit with no attachment to the globe. Re-exploration proved virtually impossible because of the scarring affecting the tissue planes and transposed vertical rectus muscles. Ultimately a full transposition of the vertical recti muscles was undertaken with an associated resection of these muscles and a satisfactory result was obtained.

INTRAOPERATIVE SNAPPING (GROUP 2)

Five muscles snapped during the course of squint surgery. These muscles had been involved in previous surgery or were associated with presumed extraocular muscle pathology (Table 2). At the time they were being held without excessive force on a muscle hook when the muscle simply tore across its belly and retracted. In case 5 the patient had undergone multiple extraocular muscle operations to the affected eye in the region of the snapped superior rectus muscle.

The muscle was noted clinically to be pale and inelastic in case 6 and the pathology report on a biopsy specimen indicated that there was an increase in the interfibre connective tissue with the presence of some abnormal muscle fibres. The inferior rectus muscle in case 7 had been involved in a blow-out fracture and the muscle had been damaged at the time of the injury.

Case 8 had undergone superior oblique resections and antero-placements for IV nerve palsies with a resultant acquired Brown's syndrome. The superior rectus muscle snapped during the second operation to correct the troublesome

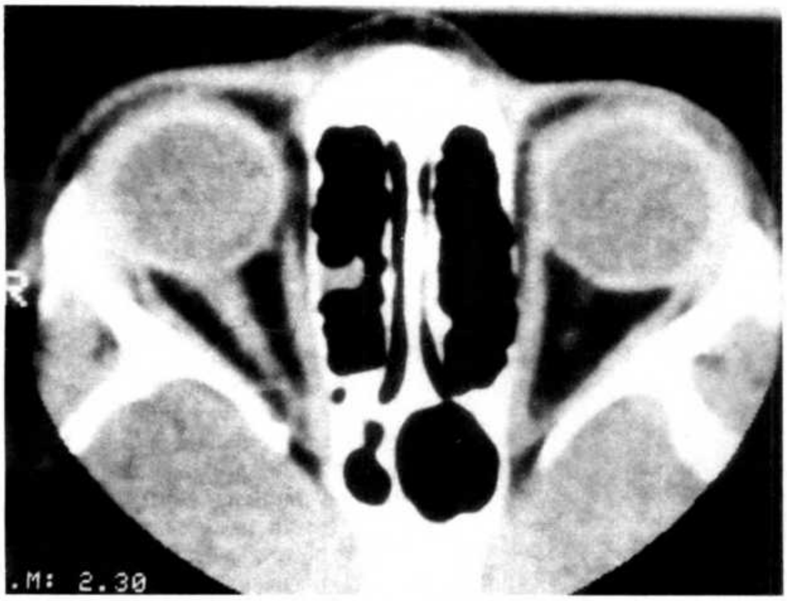


Figure 4 CT scan demonstrating that the right medial rectus remains attached to the eye by tenuous attachments.

Figure 5 Manifest exotropia with no adduction. The medial conjunctiva in the right eye is heaped up and results in a cosmetic blemish.

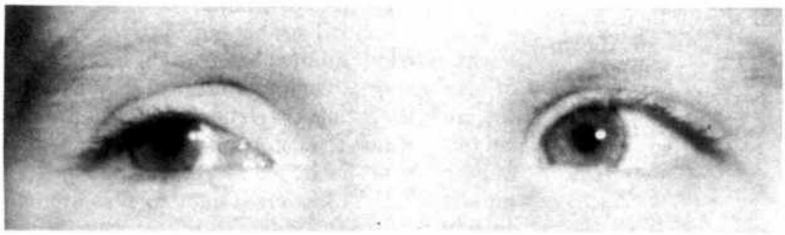


Figure 6 Maintenance of binocularity in the same child as Fig 5 is by adoption of an abnormal head posture.

Table 2 Intraoperative snapping

Case	*Pathology*	*Surgery*	*Muscle*	*Position*
5	IVN palsy previous surgery	SO tuck	SR	Relocated
6	Rubella (congenital)	MR− MR−	MR	Relocated
7	Blow-out fracture	IR− SR−	IR	Relocated
8	Previous surgery	SO	SR	Relocated
9	Long standing VI palsy after BTXA	MR−	MR	Relocated. Fragmented muscle

SO=superior oblique; BTXA=botulinum toxin A

torsion. Pathological examination demonstrated mild degenerative changes only. The last case in this group (case 10) had a long standing VIth nerve palsy (at least 30 years) and following two injections of botulinum toxin the esotropia reduced from 90 D to 45 D. The forced duction test still demonstrated a very tight medial rectus and during the attempt to recess this muscle it crumbled away from the retaining hook. The reported pathology was again of degenerative changes only with no specific features.

The affected muscle in this group was not restricted to that of the medial rectus but all four rectus muscles were involved. In all cases the muscle was successfully re-located although in one case one re-exploration was required.

POSTOPERATIVE SLIP (GROUP 3)

There were six muscles which slipped in the immediate postoperative period (Table 3). The affected muscle was the medial rectus in all cases. In three patients (cases 10, 11 and 12) the patient had undergone adjustable squint surgery and the remainder had undergone a standard non-adjustable procedure.

Re-exploration in all cases revealed that the capsule of the muscle was attached to the globe by the sutures and the belly of the muscle was found retracted inside its capsule 5–6 mm behind its intended new insertion (except case 15 in which surgical exploration was delayed for some months). The muscle was easily relocated in all cases and the postoperative results were good overall.

Immediate exploration was performed as soon as the diagnosis was made. However in case 14 the patient did not re-present himself until 2 weeks after surgery despite his mother having noted the secondary divergence and limited adduction of the left eye during the first postoperative day (Figs 7, 8). The muscle was successfully re-located but some residual postoperative limitation of adduction remained and forced duction testing at a second procedure revealed a degree of lateral rectus contracture. This was treated with recession of the lateral rectus with resultant improvement in angle and range of movement.

In case 15 the delay in exploration was longer (5 months) and the muscle was found to have slipped posteriorly to 17 mm from the limbus.

Table 3 Postoperative slip

Case	*Surgery*	*Muscle*	*Clinical course*	*Outcome*
10	LR− MR+ (adj.)	MR	Adjusted day 1. Good position. No adduction beyond midline at 1 week	Muscle relocated
11	MR− LR+ (adj.)	MR	Adjusted day 1. Good position. Diplopia all positions on day 3. Limited adduction	Muscle relocated
12	MR− LR+ (adj.)	MR	Adjusted day 1. Good position. Diplopia all positions day 2. Limited adduction	Muscle relocated
13	MR− LR+	MR	Late evening (day of surgery) straight. 1st morning postop diplopia and no adduction	Muscle relocated
14	MR− MR−	MR	1st day postop. Eye straight. Later that day noted to be exotropic (by mother). Not reviewed for 2/52	Muscle relocated limited adduction
15	MR− MR−	MR	Divergent postop. Limited adduction. Explored 5 months later	Muscle relocated 17 mm from limbus. Re-advanced

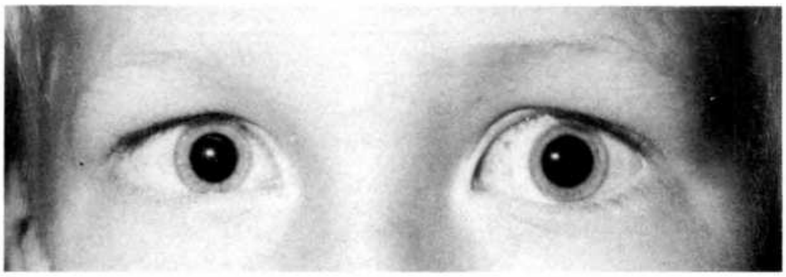


Figure 7 Secondary divergence after slippage of the left medial rectus.

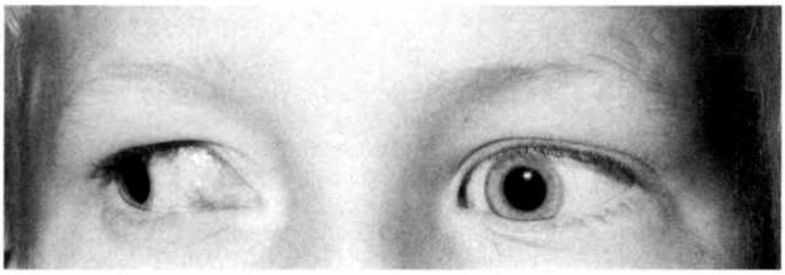


Figure 8 Limited adduction of left eye due to postoperative slip of the medial rectus (same patient as in Fig 7).

TRAUMATIC MUSCLE LOSS (GROUP 4)

Two muscles became detached from the globe during the course of an injury (Table 4). In case 16 the medial rectus muscle had become damaged in what appeared to be a blunt injury when the eye was struck with a snooker cue. The muscle was not found initially but CT scanning identified its presence and it was relocated at first re-exploration (Fig 9).

The rotating end of an electric drill injured the lateral aspect of the right eye in an industrial accident in case 17. Following this abduction was severely limited and the lateral rectus was shown on CT scan to be very thin with no insertion to the globe demonstable. This muscle was partially relocated at exploration and a satisfactory improvement of abduction was obtained.

Table 4 Traumatic muscle loss

Case	*Trauma*	*Muscle*	*Outcome*
16	Blunt injury	MR	Not found – LR recessed. Re-explored – found
17	Drill injury	LR	Partially relocated – good function

Discussion

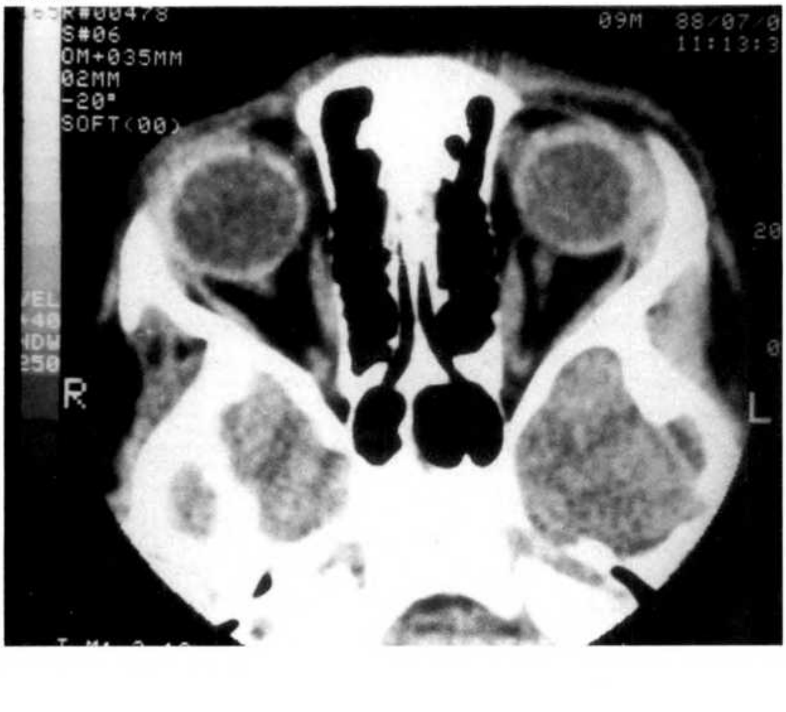
Loss of a rectus muscle can occur in a variety of different settings. Parks differentiated between the 'lost' muscle, which he characterised by the absence of any attachment of the muscle or its capsule to the sclera[1] and the 'slipped' muscle defined as a muscle which following strabismus surgery retracts posteriorly within its capsule while the empty capsule remains sutured to the sclera.[2] These definitions are based on operative findings with great emphasis being placed on the clinical similarity seen in these two different categories. Parks however does not indicate the time course of events in any of his papers on this subject and many of his patients in both categories had undergone surgery in the distant past. It is well recognised that over a period of time muscles which have undergone surgery may develop a pseudo-tendon back to their original insertion or reinsert at some point between their surgical insertion and their original insertion. In addition antagonist overaction and contraction can alter the clinical appearances over a relatively short period of time. Therefore basing these definitions on surgical findings at an undefined period of time postoperatively is not entirely satisfactory especially when the clinical findings tend to overlap to such a degree and the management is similar in both groups.

We have divided our patients differently from Parks, into four groups, based on the mechanism of loss: group 1: complete surgical severance of the muscle; group 2: traumatic break during surgery; group 3: postoperative slippage of the muscle within an intact capsule; and group 4: muscle damage by external trauma. The importance of this classification lies in its influence on the management and prognosis of the condition.

Muscles which are cut surgically, having been dissected from their surrounding fascia in the course of squint surgery, clearly have a poor prognosis for relocation (group 1). The three other categories are likely to do much better. The snapped muscles (group 2) or traumatically damaged muscles (group 4) do not rupture all of their fibres and also retain fascial attachments to the eye thus allowing them to be more easily relocated. The value of these fascial attachments to the globe is emphasised by the finding that the medial rectus was the muscle that was 'lost' in all cases in group 1. This result is in keeping with the findings of Plager and Parks who found that the majority of medial recti in their series were irretrievable.[1] The superior, lateral, and inferior recti are all attached to the globe via their adjacent oblique muscles. The medial rectus is the only muscle which can freely retract into the orbit. Undoubtedly other rectus muscles are dropped during surgery but they are usually easily found by tracing their connections to adjacent oblique muscles.

The muscle which slips postoperatively (group 3) retains an attachment to the globe in a

Figure 9 CT scan demonstrating retracted left medial rectus which retains some attachments to the eye. A tuft of muscle is seen at the insertion.



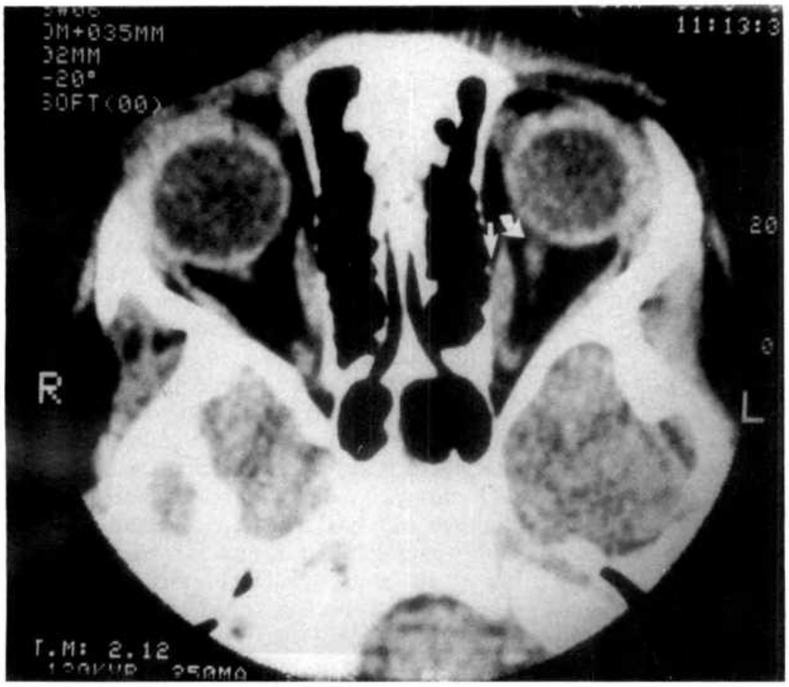


Figure 10 The line of exploration should follow the straight arrow along the medial rectus. Following around the globe leads to the optic nerve.

different manner, by means of its capsule. Postoperative slippage is a situation which occurs when the muscle is not fully included in the locking sutures.[2] Instead the suture is passed superficially into the muscle capsule but does not pass through the fibres of the muscle. This results in a satisfactory appearance and position of the muscle at the time of surgery. In the early postoperative period however when muscle function returns and the fibres contract the belly of the muscle retracts within the anchored fibrous capsule. Exploration of slipped muscles within 1 week of surgery reveals that the muscle capsule alone is attached to the globe and the muscle belly can be located posteriorly within this sheath. The characteristic clinical picture is that of an acceptable surgical result immediately postoperatively with a good range of ocular movements; however an increasing angle of squint develops with incomitance and associated limitation in rotations in the early postoperative period of hours to days.

It is interesting to note that all of our slipped muscles were medial recti. Furthermore all but one had been recessed. We are unable to determine whether the increased risk of slippage is a function of the medial rectus per se or of the muscle having been recessed. Our impression is that recession is the responsible mechanism as in this procedure the suture is passed through the insertion rather than the belly of the muscle making the placement of the suture through the muscle body less well defined.

Three of the cases of slipped muscles had surgery carried out using the adjustable suture technique. It is unlikely that the loss was due to the method used as in all cases the adjustment on the first day proved to be straightforward and adequate and it was in the period of time following this that the slippage took place.

The muscles which traumatically ruptured during surgery had other pathology or had undergone previous surgery. In no case was excessive traction or force used to hold the muscle. The muscle which snaps across its width leaves a small tuft of the insertion attached to the globe and frequently retains fibres or capsule attached to the part of the muscle which has retracted. In addition the check ligaments have not usually been dissected away. This type of damaged muscle may prove difficulty to reattach to the globe due to fragmentation of the muscle during suturing.

Losing a muscle not only results in a cosmetic problem but can cause constant diplopia in adults which may be compensated by an abnormal head posture. In addition children undergoing surgery for a potentially binocular result may lose the stimulus to develop or obtain binocular responses at a period when they are most susceptible.

Management

Any muscle lost peroperatively should if possible be retrieved during that operation as this provides the best possible chance of a good outcome. This applies both to snapped muscles and to cut muscles. At the time of surgery ideally two experienced assistants should be present to assist with the exploration. They should provide good exposure using malleable retractors to open up the fascial planes. One common problem that is frequently encountered is that the direction of search followed is around the globe rather than directly backwards along the line of the medial rectus (Fig 10). If dissection takes place around the globe then optic nerve damage is likely as this is the first structure to be encountered. To locate the medial rectus the direction of exploration should be parallel to the medial wall of the orbit following the muscle's anatomical line.

In most cases the operating miscoscope is a useful tool to help identify any muscle fibres. It is of the utmost importance that the fascial planes are not damaged when dissecting posteriorly through the muscle sleeve as orbital fat adherence and scarring can easily be produced. If the muscle cannot be identified clearly it is useful to attach the adjacent fascia to the globe and recess the ipsilateral antagonist, the amount being based on the springback test. At this stage we do not recommend that transposition surgery is carried out. If the ipsilateral antagonist has already undergone surgical recession or resection prior to loss of the muscle then the only transposition option available (to ensure against anterior segment ischaemia) is movement of the nasal halves of the inferior and superior recti to the medial rectus insertion. This procedure does not provide adequate adduction (see case 4) and in addition re-exploration of such cases is almost impossible because of scarring, adherence, and damage to the fascial planes. In essence if this operation is performed then it is extremely difficult for the future intervention to be successful. This has been recommended as the surgical procedure of choice,[2] but the resultant adduction when used for the lost medial rectus (case 4) was disappointing. Transposition of the complete superior and inferior rectus muscles medially is also unlikely to produce adequate adduction (unless combined with a resection of these vertical recti). If combined with a recession of the ipsilateral lateral rectus this procedure is likely to cause anterior segment ischaemic in adults. Therefore at this first stage we recommend recession of the ipsilateral antagonist with attachment of fascia to the medial rectus insertion as this may allow a degree of muscle activity and guide the way towards the missing muscle.

CT scanning is the investigation of choice in order to determine the exact position of the muscle and presence or absence of any attachment to the eye.

Location of the missing muscle may be assisted by utilisation of the oculocardiac reflex as follows.[5] Traction is applied to a piece of tissue in which the muscle is suspected to be present; if this tissue does contain the muscle the oculocardiac reflex will be activated leading to slowing of the pulse rate. Atropine should be withheld from the pre-medication as this will block this reflex.[5]

If the muscle cannot be found the ipsilateral lateral rectus muscle should be maximally recessed on hang-back sutures and fascia attached to the medial rectus insertion. Stay sutures should be placed through the superior and interior rectus insertions and passed through the lid medially holding the eye in maximal adduction for 6 weeks.

If the eye remains exotropic, further surgery would consist of a complete medial transposition of the vertical recti. In order to obtain any valuable degree of adduction both muscles should also have a 5 mm resection. In older patients preoperative anterior segment fluorescein angiography should be performed to assess the risks of anterior segment ischaemia. If there is any delay between operative procedures great care should be taken to assess the ocular rotations using forced duction and spring-back tests as secondary contracture, and in children sensory realignment, may continue to take place.

There are several surgical techniques which reduce the likelihood of muscle loss. These include (1) careful full thickness locking bites of each muscle suture, care being taken not to insert the sutures too superficially into capsule only; this is assisted by spreading the muscle well on a Chavasse hook; (2) removal of anterior Tenon's capsule so that the muscle can be clearly visualised; (3) multiple small cuts when detaching the muscle from the globe rather than one large snip; and (4) some authors have suggested that the majority of the posterior intermuscular septum and check ligaments should be left intact in order to allow easy relocation of a lost muscle.[6]

Management of the slipped muscle is early and careful exploration. This is important for two reasons: firstly, with regard to the timing of surgery as the fragile capsular attachments of an actively contracting muscle may not remain adherent to the globe for a long period (see case 15); and secondly, with regard to surgical technique as great care must be taken in order to prevent any further damage to or loss of these tenuous strands during exploration. If left for any period of time antagonist contraction may alter the final surgical outcome. In case 14 which was left for more than a few days postoperatively contracture of the ipsilateral antagonist was noted as early as 2 weeks following initial surgery and this required two surgical procedures to improve the final result. At exploration the empty capsule is a translucent structure which can usually be identified by the attached sutures. The recoiled muscle is found by following the capsular sleeve posteriorly.

The diagnosis of a traumatically ruptured or lacerated muscle is based on the history in association with CT scan results and the findings at surgery. In patients with traumatic extraocular muscle imbalance this injury must be differentiated from the restrictive type of abnormality seen in blow-out fractures or weakness secondary to haematoma formation. The muscle may be damaged either as a result of blunt or penetrating trauma. CT scans are essential in making the diagnosis and in determining the location of the muscle prior to exploration.

In summary there are different mechanisms of extraocular muscle loss with different likely outcomes. Relocation of the slipped, snapped, or traumatically ruptured or severed muscle is in general successful. The medial rectus muscle which is lost during squint surgery causes particular problems in relocation.

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Uveitis and systemic disease

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Abstract

A prospective study was conducted of 865 patients with uveitis to determine the frequency of associated systemic diseases and to assess the value of limited laboratory screening of these patients. All patients underwent a standard diagnostic protocol followed – when indicated – by special tests and procedures performed in order of likelihood ('tailored approach'). For 628 patients (73%) a specific diagnosis was established based on history, ophthalmologic examination, and laboratory and radiographic studies. A definite association with systemic disease was determined for 220 patients (26%). A relationship with a subclinical systemic disorder could be presumed in 201 cases (23%) and a well-established clinical uveitis entity without a recognisable systemic disorder was present in 207 cases (24%). For 237 patients (27%) a diagnosis could not be determined. The most frequently observed systemic diseases were sarcoidosis (7%) and HLA-B27-associated seronegative spondylarthropathies (6%). Presumed or definite toxoplasmosis was encountered in 10% of cases. HLA-B27-associated acute anterior uveitis was the most common clinical entity (17%). In the majority of cases the presence of a systemic disease was not suspected prior to eye involvement and was only recognised after the subsequent diagnostic procedures.

Uveitis is a general term for inflammation of the uveal tract due to any cause and usually includes a large group of diverse diseases affecting not only the uvea but also the retina and vitreous. The aetiology is difficult to establish since the exact cause of uveitis frequently remains unknown.

Therefore the current International Uveitis Study Group classification system is based on the anatomical location of the inflammation: anterior uveitis (iris and ciliary body), posterior uveitis (choroidea and retina), intermediate uveitis (peripheral retina and pars plana of the ciliary body), and panuveitis (generalised inflammation of the whole uvea).[1] The differential diagnosis for uveitis depends on the type of uveitis involved and various geographical, environmental, and population factors; moreover it continues to change as new entities are recognised and improved diagnostic techniques become available.[2]

Uveitis is not a single disease but includes ocular involvement related to various systemic disorders as well as primary ocular conditions. The association of uveitis and systemic disease is well known. In earlier studies the majority of cases were attributed to tuberculosis and syphilis whereas recent reports show an association with various generalised diseases.[2-10]

We conducted a prospective study to assess the frequency and type of systemic diseases associated with intraocular inflammation using a standard diagnostic evaluation in a large group of patients.

Table 1 *Screening of uveitis patients*

	Anterior uveitis	Intermediate and posterior uveitis	Panuveitis
ESR, red and white blood cell count, glucose	+	+	+
HLA-B27	+	−	+
Angiotensin converting enzyme, lysozyme	+	+	+
Lues serology	+	+	+
Antinuclear antibodies*	+	−	+
Chest radiography	+	+	+

*Only in children under 16 years.

Patients and methods

The study included 881 consecutive patients with uveitis who visited the Ophthalmologic Department of the Academic Medical Centre in Amsterdam between 1984 and 1989. Sixteen patients were not available for follow-up; therefore 865 uveitis patients could be evaluated. AIDS patients were not included in this study. Our institution combines secondary and tertiary ophthalmic care: patients are referred by ophthalmologists from a large area and also by general practitioners from a smaller local area.

Complete ophthalmic examination was performed in all cases. The assessment included a visual acuity test, slit-lamp examination, indirect funduscopy, posterior pole evaluation with a 90 dioptre lens, and intraocular pressure measurements. The results of the ophthalmic and laboratory examinations were stored in a computer databank.

The diagnostic criteria for uveitis were those laid down by the International Uveitis Study Group.[1] The diagnostic category intermediate uveitis describes the anatomical position of an intraocular inflammation. A (classic) subset of intermediate uveitis with the inflammatory focus in the peripheral retina and cystoid macular oedema without evidence of general disease was called pars planitis.

All patients underwent a standard screening protocol depending on the ophthalmic anatomical classification (Table 1). Selected patients (depending on the history, character and activity of their ocular disease, as well as the outcome of the laboratory and radiographic screening procedures) underwent special tests and diagnostic procedures ('tailored approach'). These tests included HLA-A29 and HLA-B5 typing, radiography of the sacroiliac joints and

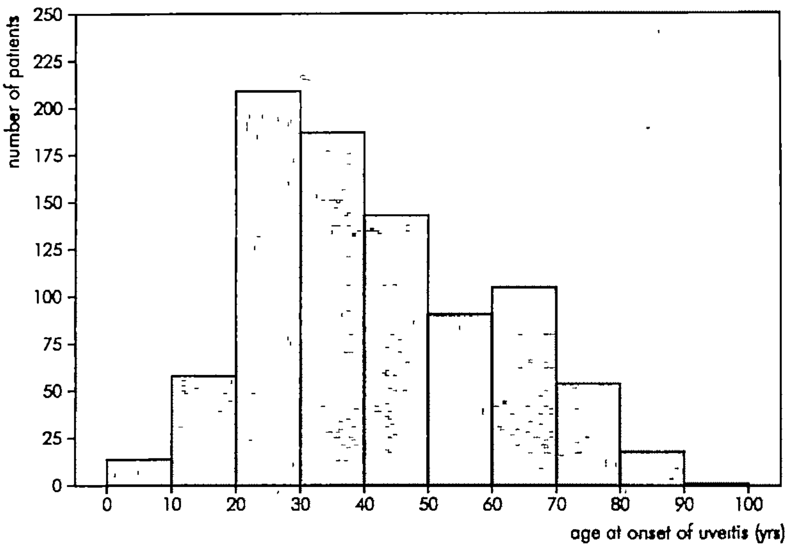

Figure 1 Age at onset of uveitis.

skull, computed tomographic (CT) brain scanning, gallium-67 whole body scintigraphy, conjunctival and lacrimal gland biopsy, Mantoux test, and aqueous humour analysis for evidence of intraocular synthesis of specific antiparasitic and antiviral antibodies.

The diagnosis of presumed ocular toxoplasmosis was based on the clinical observation of unilateral focal necrotising retinitis sometimes associated with typical old pigmented scars. *Toxoplasma* serology was not routinely performed since anti-toxoplasmal antibodies are present in the majority of the Dutch population, therefore positive titres in adults have no diagnostic value.[11] In doubtful cases the intraocular production of anti-toxoplasmal antibodies was assessed by aqueous humour analysis (Goldmann-Wittmer Coefficient).[12] Radiography or CT scanning of the skull was performed only when patients with ocular toxoplasmosis had neurological symptoms. Systemic toxoplasmosis was diagnosed in the event of clinical evidence of extraocular involvement. The diagnosis of acquired ocular toxoplasmosis was based on the presence of focal necrotising retinitis and a more than four-fold rise of the antibody titre together with specific IgM antibodies in the circulation. Congenital toxoplasmosis was the established diagnosis for neonates with focal retinitis and positive serological findings.

The diagnosis of sarcoidosis was always confirmed by histological examination of biopsy specimens. Depending on the signs of the disease a biopsy was obtained from lungs, peripheral or mediastinal lymph nodes, conjunctiva, lacrimal gland, or liver. When none of these organs were clinically involved the biopsy was not attempted. We did not perform the Kveim test. Presumed ocular sarcoidosis was diagnosed when uveitis patients had chest radiographic or gallium-67 scintigraphic patterns typical of sarcoidosis and/or increased serum levels of angiotensin-converting enzyme (above 60 U/l)[13] without however histological evidence of the disease.

All HLA-B27 positive patients with anterior uveitis who had complaints of the peripheral joints or low back pain were examined by the rheumatologist. The diagnosis of ankylosing spondylitis was established when the patients fulfilled the criteria described by Bennet and Burch.[14] The criteria proposed by Lee *et al* were used for the diagnosis of Reiter's syndrome.[15]

All other systemic diseases were diagnosed according to current diagnostic criteria; the patients were also examined by the respective specialists.

We used the χ^2 test for statistical analysis; $p<0{\cdot}01$ was considered significant.

Table 2 Classification of uveitis patients according to anatomic position

	No	%
Anterior uveitis	471	54·5
Intermediate uveitis	76	9·0
Posterior uveitis	142	16·5
Panuveitis	176	20 0
Total	865	100

Table 3 Systemic disease in uveitis patients

	All uveitis patients (n=865)	*Anterior uveitis (n=471)*	*Intermediate uveitis (n=76)*	*Posterior uveitis (n=142)*	*Panuveitis (n=176)*
Systemic disease	220	118	8	34	60
Sarcoidosis	59	23	3	8	25
Seronegative spondylarthropathies	48	44	0	0	4
Diabetes mellitus*	20	20	0	0	0
Tuberculosis	12	6	0	2	4
Toxoplasmosis with extraocular manifestations	9	0	0	7	2
Juvenile rheumatoid arthritis	8	8	0	0	0
Behçet's disease	7	0	0	1	6
Lues	6	5	0	0	1
Multiple sclerosis	6	0	4	0	2
Miscellaneous	45	12	1	16	16
Presumed systemic disorder	201	110	4	67	20
HLA-B27 associated, without rheumatic disease	105	105	0	0	0
Presumed ocular toxoplasmosis	74	0	0	62	12
Presumed ocular sarcoidosis	22	5	4	5	8
Specific ocular disease†	207	88	52	19	48
Undetermined	237	155	12	22	48

*Diabetes mellitus in nine additional patients was considered not related to their uveitis
†See Table 4

Results

The mean age at onset of uveitis was 42 years (range 3–91 years). The peak age of onset of uveitis occurred in the third and fourth decades; 45% of our series presented between 20 and 40 years of age (Fig 1). The male:female ratio was 1:1 for the entire series as well as for all anatomical categories of uveitis. Our study included 83 (10%) black patients (the country of origin being mainly Surinam), 38 (4%) oriental patients (predominantly from Indonesia) and 40 (5%) patients from the Mediterranean Basin.

In this series anterior uveitis was the predominant clinical type (471 cases, 54·5%); 176 (20%) patients presented with panuveitis, 142 (16·5%) with posterior uveitis, and 76 (9%) with intermediate uveitis (Table 2).

The specific diagnosis for our patients with uveitis is shown in Table 3. For 220 (26%) of the 865 patients the intraocular inflammation was considered to be causally related to the systemic disease. Systemic diseases most frequently associated with uveitis included sarcoidosis (59/865; 7%) and HLA-B27 associated seronegative spondylarthropathies (48/865; 6%). Syphilis and tuberculosis were responsible for 0·6% (6/865) and 1·4% (12/865) of all cases respectively. Toxoplasmosis with clinical extraocular mani-

Table 4 Specific ocular diseases among uveitis patients

	All uveitis patients (n=207)	*Anterior uveitis (n=88)*	*Intermediate uveitis (n=52)*	*Posterior uveitis (n=19)*	*Panuveitis (n=48)*
Fuchs' heterochromic cyclitis	53	30	0	0	23
Pars planitis	52	0	52	0	0
Idiopathic vasculitis	19	0	0	14	5
Viral uveitis*	39	24	0	2	13
Posner-Schlossman syndrome	8	8	0	0	0
Miscellaneous	36	26	0	3	7

*Included are cases with herpes zoster uveitis (clinical diagnosis), herpes simplex and Epstein-Barr virus uveitis (proven by aqueous humour analysis), and eight patients with acute retinal necrosis.

festations comprised 1% (9/865) of the series, whereas presumed toxoplasmosis accounted for 9% (74/865). For 12 patients the diagnosis of definite congenital toxoplasmosis could be confirmed. Acquired ocular toxoplasmosis was observed in four patients all of whom were receiving immunosuppressive drugs during the onset of uveitis (three patients for various malignancies and one after renal transplantation).

In 201 (23%) cases a systemic disease was presumed without however, the clinical evidence of extraocular involvement required for diagnosis. The HLA-B27-positive acute anterior uveitis patients who did not fulfil the criteria required for the diagnosis of ankylosing spondylitis and patients with presumed congenital toxoplasmosis or sarcoidosis were included in this group.

For 207 (24%) patients a specific ocular disease was diagnosed without an underlying systemic disorder and included 53 (6%) patients with Fuchs' heterochronic cyclitis and 52 (6%) patients with classic pars planitis (Table 4). In the remaining 237 (27%) cases uveitis was not associated with a systemic disorder but was also not characteristic of a recognised type of uveitis.

Among patients with anterior uveitis HLA-B27-associated acute anterior uveitis was the most frequently diagnosed entity (149/471; 31%) with a male predominance (male:female ratio was 1·4:1, $p<0\cdot05$). Anterior uveitis was considered to be related to diabetes mellitus in 4·3% of patients.[16] In nine additional patients diabetes mellitus was observed although another aetiology was established for the uveitis. Miscellaneous systemic diseases in patients with anterior uveitis included gonorrhea, schistosomiasis, lepra, loiasis, ornithosis, and leukaemia.

Eight of 76 (10·5%) patients with intermediate uveitis had a recognisable systemic disease (four had multiple sclerosis, three sarcoidosis and one Lyme borreliosis). Pars planitis with peripheral vitreous opacities and snowbanking without evidence of systemic disease was observed in 52 (68%) of 76 patients with intermediate uveitis.

Toxoplasmosis (systemic and presumed ocular) was the most frequently diagnosed disease in the posterior uveitis group (69/142 patients, 49%) whereas sarcoidosis was more common in the panuveitis group (biopsy proved and presumed; 33/176 patients, 19%). Miscellaneous diseases in the posterior and panuveitis groups included autoimmune diseases such as systemic lupus erythematosus, mixed connective tissue disease, Wegener's disease, essential cryoglobulinaemia as well as Vogt-Koyanagi-Harada syndrome, subacute sclerosing panencephalitis, candidiasis, toxocariasis, and Lyme borreliosis.

Of the seven Behçet patients, five were from the Mediterranean Basin ($p<0\cdot001$) and of the 59 patients with sarcoidosis 22 (37%) were black ($p<0\cdot001$).

Fifteen of 59 (25%) patients with biopsy-proved sarcoidosis were known to have this disease before the onset of uveitis; for 44 (75%) patients the diagnosis was established after the onset of uveitis. In five cases initial screening for sarcoidosis was negative and the diagnosis was not proved until more than 1 year after the onset of ocular symptoms.

The diagnosis ankylosing spondylitis was established before the onset of uveitis for 16 of 41 (39%) patients; for the remaining 25 (61%) patients the diagnosis was made during the uveitis work-up. Of seven patients with Reiter's syndrome three were known to have this disease before the onset of uveitis.

Discussion

In this prospective study of 865 patients the specific diagnosis for an intraocular inflammation was established in 73% of all cases. Systemic disease, which could be considered to be causally related to the intraocular inflammation, was diagnosed in 26% of all cases on the basis of the standard initial screening protocol followed by a 'tailored' diagnostic approach. In an additional 23% of all cases the presence of a systemic disorder was presumed. The majority of our patients were not known to have systemic disease prior to the ocular symptoms and the diagnosis was not established until the uveitis work-up.

The reported frequency of a systemic disease underlying uveitis in the last two decades varies from less than 19% to 46%.[2, 6-8, 10, 17] The study with the lowest frequency involved 120 new uveitis patients from northern Finland predominantly with anterior uveitis (88%); there was no specified diagnostic protocol and the aetiological factors studied were mainly of infectious origin.[17] The highest frequency of systemic disease was found for 368 uveitis patients in hospital in London (58% had anterior uveitis); ocular toxoplasmosis, the most common entity, was classified as a systemic disorder.[6] In a report of 236 patients with uveitis who were referred for a medical examination to an internist, Rosenbaum found systemic disease in 40% of patients; the highest frequency was found for Reiter's syndrome (7·2%) followed by sarcoidosis (5·5%) and ankylosing spondylitis (5·5%).[10] The extensive series of Henderly *et al* included a retrospective analysis of 600 referred patients 22% of whom had systemic disease (patients with toxoplasmosis were not included; 7%); 4% had sarcoidosis.[2]

Comparison of uveitis statistics from various countries is very difficult. A large survey comparing the pattern of uveitis in London and Iowa revealed no major differences (histoplasmosis was excluded).[7] In another series of 240 Chinese patients with uveitis Behçet's disease was responsible for 18% of all cases.[18]

Several factors may contribute to the variation in reported incidence of the various systemic diseases underlying intraocular inflammation. The true geographical differences as well as the selection of patients, author's interest, diverse diagnostic investigations, and criteria influence the results of the studies. Most published reports are retrospective and concern only those patients in hospital or otherwise selected. The racial and age distributions are not always specified and the laboratory tests for uveitis patients are usually not consistent. Another potentially important factor that could play a role in the reported discrepancies are the criteria used for diagnosis of the specific systemic disease. The fact that our hospital is in part a referral centre helps to explain the bias of the present study.

In addition the reported incidence of various diseases may be distorted due to confusion about the nomenclature used for uveitis patients. The descriptive anatomical classification system and the aetiological diagnosis are frequently used together in a single coding system which is not correct in our opinion. An anatomically defined uveitis entity (for example anterior uveitis) may include different causes and associations (lues, viral infection, sarcoidosis, ankylosing spondylitis, Reiter's syndrome, and so on) while the aetiological diagnosis does not always indicate the localisation of the inflammatory process. The descriptive and aetiological approaches do not exclude one another and in our view should be used separately as we have done in this present series.

In this study the anatomical entity most frequently associated with definite systemic disease was panuveitis (34%) followed by anterior uveitis (25%). Anterior uveitis was reported by Rosenbaum to be the one most likely to be associated with systemic disease (53%);[10] however other studies do not confirm this high rate of association.[2,8,17] These differences were attributed to the different referral patterns which lead to different representations of the various types of uveitis. In our study 25% (118/471) of patients with anterior uveitis had systemic disease (predominantly ankylosing spondylitis) and 22% patients (105/471) with acute anterior uveitis were HLA-B27 positive without a well defined associated systemic disease (Table 3). Although many of the latter had complaints suggesting related rheumatic disease they did not fulfil the required diagnostic criteria.

The most frequently observed systemic disease among our uveitis patients was (histologically proved) sarcoidosis (7%); this percentage is somewhat higher than that reported in previous studies. The higher frequency of sarcoidosis found in this study could be explained by our systematic assessment of both angiotensin-converting enzyme and lysozyme levels as well as chest *x* rays in all cases followed by examination of biopsy specimens when sarcoidosis was suspected.

The differential diagnosis for uveitis continues to change. Recently Lyme borreliosis was found to cause diverse ocular symptoms including scleritis, vitritis, retinitis, and papillitis.[19,20] The two patients with ocular Lyme borreliosis in our series were diagnosed during the last year of the study; however a systematic search for this disease was not carried out in the preceding years. The exact frequency of Lyme disease among patients with intraocular inflammation is not yet known.

The search for a systemic disease in patients with uveitis is a controversial subject. It is generally agreed that extensive unfocused laboratory screening is inefficient and very costly and that a patient with uveitis who has general medical examination will undergo physical and laboratory examinations which will not contribute to the correct diagnosis of the disease underlying the uveitis.[21] In this study we used a limited screening protocol based on the anatomical classification of the uveitis and systemic diseases that could cause the intraocular inflammation. Subsequent diagnostic procedures were planned depending on the suspected diagnosis. This 'tailored' approach demands that a precise history be taken and careful examination be performed.

The changing pattern of uveitis due to the eradication of various diseases and the recognition of new diseases and advance in diagnostic techniques implies a change in the diagnostic approach to uveitis. Laboratory tests performed with peripheral blood from patients with intraocular inflammation may not be discriminatory. For infectious types of uveitis negative blood test results can sometimes be used to exclude the suspected diagnosis but one may not conclude that a specific disease is the cause of an ocular ailment when peripheral blood yields a positive test result.[21] The aqueous or vitreous analysis is therefore becoming indispensable especially for the infectious types of uveitis.

In this prospective study we established a specific diagnosis for the majority of uveitis patients, 26% of whom had a definite systemic disease; for an additional 23% of patients a relationship with a subclinical systemic disorder could be presumed. To obtain such a diagnosis a complete ophthalmic examination with a detailed history and the 'tailored' diagnostic approach are essential.

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FIFTY YEARS AGO

Phlyctenular ophthalmia

It is concluded that phlyctenular ophthalmia is a manifestation, not of tuberculous disease, but of tuberculous infection, the phlycten making its appearance only when a hyperallergic phase is present and there is a suitable (? specific) exciting factor of endogenous or exogenous origin. It is suggested that the age distribution, sex-incidence and seasonal variation seen in phlyctenulosis are best explained on the assumption that the affection is tuberculous in character. The prognostic significance of the phlycten is graver than that of a positive tuberculin reaction in a child; this is borne out by the subsequent incidence of tuberculosis and mortality from it in children previously affected with phlyctenulosis. – From 'The aetiology of phlyctenular ophthalmia,' by Arnold Sorsby. *Br J Ophthalmol* 1942; 26: 211.

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Haemorheological parameters in patients with retinal artery occlusion and anterior ischaemic optic neuropathy

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Abstract

The haemorheological parameters haematocrit (Hct), plasma viscosity (PV), red cell aggregation (RCA), red cell filterability (RCF), apparent whole blood viscosity (WBV), and fibrinogen were measured in 31 patients with retinal artery occlusion (RAO), 25 patients with anterior ischaemic optic neuropathy (AION), and 19 patients with giant cell arteritis (GCA). The patient groups were compared with controls of same age and similar prevalence of cardiovascular risk factors. Patients with RAO and AION have a significantly decreased RCF in comparison with controls. All other parameters showed no differences. Patients with GCA had significantly decreased Hct and RCF and increased PV and fibrinogen. After 2 weeks of systemic treatment with high dose steroids in patients with GCA the plasma viscosity had returned to normal and was even lower than in controls, and the Hct and fibrinogen had reached normal levels.

Arterial occlusions of the eye are usually acute events followed by an alarming diminution of visual acuity with only few or no possibilities of a therapeutic reversal. This specially applies to the severe reduction of retinal function caused by acute retinal artery occlusion (RAO).[1-3] The limited survival time of the retinal tissue in relation to visual acuity requires an immediate initiation of therapy, but there is still no treatment scheme that has gained wide acceptance. Non-arteritic anterior ischaemic optic neuropathy (AION) characteristically causes precipitous visual loss[4 5] accompanied by partial visual field loss in about 50% of eyes, probably due to occlusion of posterior ciliary arteries. The arteriosclerotic origin of both diseases is probable, but further investigations into the pathophysiology of this disease are necessary to develop new therapeutic concepts.

Giant cell arteritis (GCA) often leads to severe visual loss caused by inflammatory occlusion of the central retinal artery or posterior ciliary arteries. The accepted therapy in this disease is systemic treatment with high dose steroids. However sometimes visual loss or striking of the second eye cannot be prevented despite immediate therapy.[6] This may depend on a changed haemorheological situation as increased fibrinogen concentrations and decreased haematocrit (Hct) are constant features of this disease.[7]

The possible role of haemorheological factors in the development of arterial occlusions of the eye has been pointed out by Wiederholt,[8] but so far only Kiesewetter *et al*[9] and Wolf *et al*[10] have presented data on rheological findings in patients with RAO, detecting slight haemorheological abnormalities in these patients. To our knowledge no measurements of blood fluidity have been obtained from patients with non-arteritic AION and GCA. Improvement of blood fluidity by isovolaemic haemodilution in RAO produced conflicting results in pilot studies,[8 9 11] but preliminary data of a randomised study on this treatment modality in non-arteritic AION seem quite promising.[12]

The aim of the study was to elucidate a possible role of systemic haemorheological factors in different arterial occlusions of the eye. We investigated patients with atherosclerotic and arteritic occlusions of retinal and ciliary arteries and measured four basic haemorheological parameters (haematocrit (Hct), plasma viscosity (PV), red cell aggregation (RCA), red cell filterability (RCF)) and additionally the apparent whole blood viscosity (WBV).

Materials and methods

All patients with recent RAO, AION, and GCA referred to the Augenklinik, Klinikum Steglitz, Free University Berlin, from 1985 to 1989, were considered for a prospective inquiry.

Every patient underwent a physical examination, ECG, chest *x* ray and a laboratory routine check-up. In addition patients were submitted to a detailed ophthalmological examination and funduscopy.

We performed the following rheological measurements: Hct with micromethod, PV with a capillary viscosimeter, RCA with a Myrenne aggregometer, RCF with a Myrenne MF4 (nucleopore filters of 5 μm pore diameter), apparent whole blood viscosity with a Wells-Brookfield cone plate microviscometer. The rheological measurements are described in detail elsewhere.[13] The results of RCA are given after the blood sample was disaggregated with 600/s for 5 s and then aggregation was measured at a stop to 0/s. Values are without dimension. WBV was measured at six different shear rates. In our results we only give the value at 23/s, measurements at lower shear rates were discarded because they are less reliable.[14 15] Fibrinogen concentration was measured in the routine laboratory of the clinic (method: Clauss, fibrinogen standard curves by Merz and Dade) and compared with the normal values of the laboratory.

The systemic treatment of patients with GCA with prednisolone was begun with an oral dose of 200–400 mg/day and reduced within 14 days to

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75–50 mg/day. In these patients the rheological measurements were repeated after 14 days' treatment.

The rheological data were compared with controls of same age and with similar prevalence of cardiovascular risk factors. The controls were recruited from patients without vascular diseases of the eye, but who were to undergo surgery for cataract or retinal detachment; they are described elsewhere.[13]

STATISTICAL ANALYSIS

Statistical variations of the results are expressed as standard deviation of the mean (SD). The Student's t test was used for comparison of two means. RCF has additionally been tested by the U test of Mann, Whitney and Wilcoxon, which is not dependent on a normal distribution of the variables. Significant differences were considered to be present with $p<0{\cdot}05$.

Results

We measured basic rheological data in 31 patients with RAO (14 women, 27 central and four branch artery occlusions) aged 70·4 (12·9) years (40–95 years), 25 patients with AION (12 women) aged 65·5 (9·0) years (51–83 years) and 19 patients with GCA (15 women) aged 76·1 (5·3) years (62–84 years). We compared the measurements with the data of 20 control subjects (10 women) aged 68·1 (10·3) years.[13] There were no significant differences between the patient groups and the controls in age and risk factors (Table 1) except in patients with GCA, who had a significantly higher age than controls ($p<0{\cdot}05$) and a larger proportion of women.

Table 2 shows the results of haemorheological measurements in patients with RAO and AION in comparison with control subjects. We found no significant differences in Hct, PV, RCA, WBV, and fibrinogen concentration. Measurements of WBV with shear rates of 230, 115, and 46/s show a significant decrease ($p<0{\cdot}05$) in the two patient groups (not given in the table), probably due to a somewhat lower Hct. The values of RCF in both patient groups were significantly decreased compared with controls ($p<0{\cdot}01$).

*Table 1 Number, sex, age (SD) and portion of subjects with two or more cardiovascular risk factors**

	RAO	*AION*	*GCA*	*Controls*†
Number	31	25	19	20
Women/men	14/17	13/12	15/4	10/10
Age (years)	70·4 (12·9)	65·5 (9·0)	76·1 (5·3)‡	68·1 (10·3)
Risk factors (%)	52	50	45	55

*Risk factors include high blood pressure, hyperlipoproteinaemia, smoking, obesity, diabetes mellitus, cardiovascular disease in patients with retinal artery occlusion (RAO), anterior ischaemic optic neuropathy (AION), giant cell arteritis (GCA) and in control subjects.
†Published in ref 13
‡Significant difference compared with controls.
$p<0{\cdot}05$

Table 2 Rheological data (SD) in patients with retinal artery occlusion (RAO), anterior ischaemic optic neuropathy (AION) and control subjects

	RAO	*n*	*AION*	*n*	*Controls*	*n*
Hct/W (%)	41·9 (3·5)	14	41·6 (3·2)	13	42·0 (2·3)	10
Hct/M (%)	43·1 (4·5)	17	43·7 (3·1)	12	46·3 (3·6)	10
PV (cSt)	1·35 (0·08)	31	1·33 (0·09)	25	1·37 (0·10)	20
RCA (-)	7·7 (1·8)	31	7·4 (2·0)	25	7·0 (1·4)	20
RCF (-)	19·6 (8·3)†	26	16·7 (7·6)†	22	26·4 (4·9)	17
WBV (cP)	6·6 (0·9)	31	6·7 (1·1)	25	7·4 (1·4)	20
Fibrinogen (g/l)	3·47 (0·92)	23	3·33 (0·84)	15	2·41 (0·55)*	502

Hct=haematocrit (W=women, M=men), PV=plasma viscosity, RCA=red cell aggregation, RCF=red cell filterability, WBV=whole blood viscosity (shear rate: 23/s) with natural (unchanged) Hct, and fibrinogen concentration.
*Reference value of the laboratory
†$p<0{\cdot}001$ in comparison with controls.

Table 3 and Fig 1 present the results of measurements in patients with GCA before and after 2 weeks of treatment with systemic steroids in comparison with controls. Hct was significantly decreased in all patients, which is a well known feature of GCA, due to an infection anaemia. The difference from controls might be increased by the larger portion of women in the patient group (15 of 19) as women have a lower Hct (about 4%) than men. Along with a significant increase in fibrinogen concentration the PV was elevated in comparison with controls, RCF was decreased, but despite these changes in Hct, PV, and RCF the WBV was not significantly different compared with controls. As a typical sign of GCA the ESR was significantly elevated.

After steroid treatment ESR has normalised, as had the Hct. PV decreased significantly ($p<0{\cdot}001$), to even lower levels than in controls ($p<0{\cdot}05$), RCF remained unchanged after therapy although Hct had normalised. WBV diminished significantly with steroid therapy in comparison with controls ($p<0{\cdot}01$), probably because of reduced PV, thus resulting in an overall better haemorheological situation for the patients.

Discussion

The role of systemic haemorheological factors has only partly been investigated in patients with acute arterial occlusions of the eye.[9-11 16] Hence, the aim of the study was to check the importance of such factors in different arterial occlusions of the eye. We investigated patients with atherosclerotic and arteritic occlusions of retinal and ciliary arteries and measured four basic haemorheological parameters (Hct, PV, RCA, RCF) and additionally the apparent WBV. These are the first determinations of haemorheological parameters in patients with AION and in GCA. As it is known that cardiovascular risk factors may influence blood rheology[17 18] we compared the data of the patients and control subjects with similar prevalence of cardiovascular risk factors.

In patients with RAO we only found a lower RCF; all other parameters did not show differences from control subjects. This contrasts with results of Kiesewetter *et al*[9] and Wolf *et al.*[10] These authors reported a normal erythrocyte deformability but an elevated PV (due to higher fibrinogen levels) and increased RCA in six patients with central RAO. The very low number of patients investigated make these results preliminary and different rheological methods (single erythrocyte passage time vs RCF, yield stress vs WBV) do not allow a proper comparison. Furthermore Kiesewetter *et al*[9] did not define their 'healthy' controls or give the occurrence of cardiovascular risk factors in patients and controls. This is also a likely explanation for the different results obtained.

Wolf *et al*[10] measured rheological parameters

Table 3 Rheological data (SD) of patients with giant cell arteritis (11 patients with AION, four with RAO and four without visual decrease) before treatment (GCA_0) and after 2 weeks of steroid therapy (GCA_2) in comparison with control subjects

	GCA_0	n	GCA_2	n	Controls	n
Hct (%)	37·8 (4·8)	19	41·8 (3·4)	17	44·2 (3·7)	20
PV (cSt)	1·59 (0·14)	20	1·3 (0·1)	19	1·37 (0·1)	20
RCA (-)	5·9 (1·7)	19	6·5 (1·5)	18	7·0 (1·4)	20
RCF (-)	17·7 (10·7)*	18	15·9 (12·2)*	16	26·4 (4·9)	17
WBV (cP)	6·4 (1·3)	19	5·5 (0·6)†	18	7·4 (1·4)	20
Fibrinogen (g/l)	5·28 (1·49)	11	NT		2·41 (0·55)‡	502
ESR (mm/h)	89 (24)	18	17 (9)	17		

For other abbreviations see Table 2.
NT=not tested.
*$p<0·05$, †$p<0·01$ in comparison to controls.
‡Reference value of the laboratory.

in 40 patients with retinal artery occlusion. In comparison with our results they found elevated PV in the patient group. But the values of their patients were compared with the data of controls without any cardiovascular risk factors.[15] Comparing the absolute values of PV in Wolf's and our patient group there is no significant difference. Wolf *et al* did not find decreased RCF as we did. This may also be due to different methods (single erythrocyte passage time vs RCF). Measurements of the filterability of erythrocytes are still a matter of much controversy[19 20] and technical problems have still not been solved, so these different results may be caused by methodical problems. The meaning of our finding of a decreased RCF is not quite clear, especially as it does not influence the WBV in medium shear rates. It might support the use of pentoxyfylline, which is known to improve blood filterability,[21] but up to now has not been shown to be an effective treatment in arterial occlusions of the eye.

The pathogenesis of the non-arteritic AION has not been firmly established, but a posterior ciliary vaso-occlusive process is postulated as the initial event.[5] This is supported by the finding that AION tends to occur in the age group most susceptible to the manifestations of atherosclerotic vascular disease,[22-24] and fluorescein angiography has shown delayed perfusion of the peripapillary choroid in this disease.[25 26] To our knowledge no rheological measurements have been carried out in patients with non-arteritic AION. In comparison with age and risk factor matched control subjects we only found decreased RCF in the patient group; all other rheological parameters showed no significant differences.

In patients with GCA in comparison with control subjects with similar risk factors we found unchanged WBV along with elevated PV (which should increase WBV) and diminished Hct (which should decrease WBV). The limitations of the method we applied for measurements of WBV, however, do not exclude rheological abnormalities in low flow states with shear rates below 11·75/s.[13] After systemic treatment with steroids WBV was significantly decreased due to normalised PV. This occurred despite an increased Hct. These results show that treatment with steroids not only lowers the inflammation of the vessel walls, but may have a beneficial effect on microcirculation also by improving blood fluidity. In some cases even an immediate vigorous treatment with steroids cannot avoid visual loss. The reduction of an elevated fibrin-

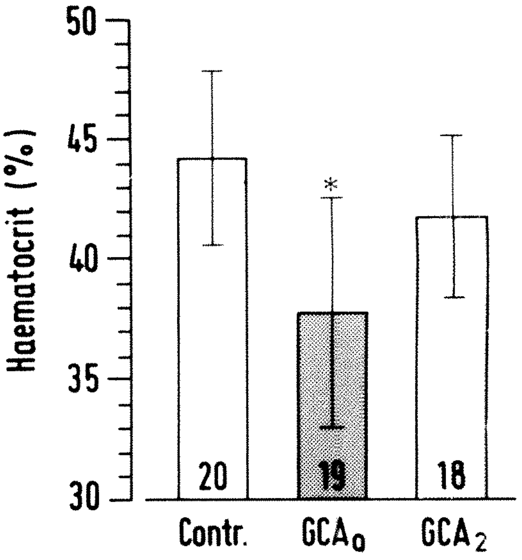

Fig 1A

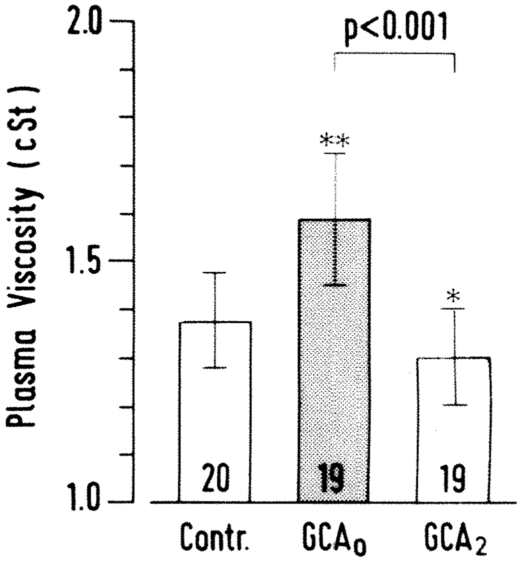

Fig 1B

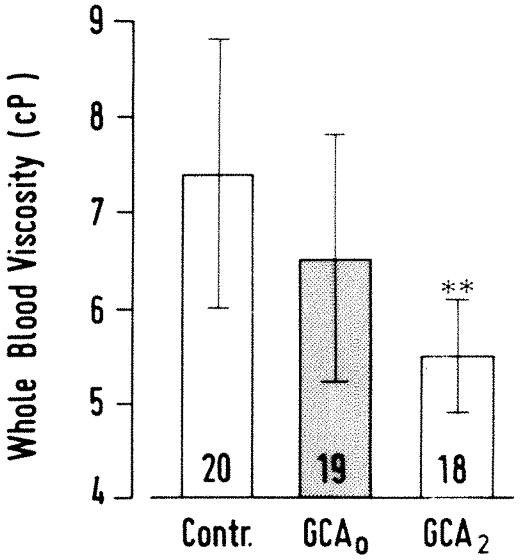

Fig 1C

*Figure 1 Haematocrit (A), plasma viscosity (B), and whole blood viscosity (C) of patients with giant cell arteritis before (GCA_0) and after 2 weeks of steroid treatment (GCA_2) in comparison with control subjects. All values are given as mean (SD). Numbers of patients are given within the bars. *=$p<0·05$, **=$p<0·01$.*

ogen concentration (leading to reduced PV) by steroids takes some days because of the half-life of fibrinogen and may thus prolong a profoundly disturbed microcirculation. Thus in cases with markedly elevated fibrinogen concentration one should think about an additional therapy with ancrod,[27 28] which lowers fibrinogen within hours.

In conclusion, our study has demonstrated only minor systemic rheological abnormalities in patients with non-arteritic RAO and AION and distinct changes in GCA in comparison with patients with similar prevalence of cardiovascular risk factors. It should be kept in mind, however, that patients with cardiovascular risk factors have an abnormal blood rheology.[17 18] Furthermore lack of measurable systemic rheological changes does not exclude local changes of fluidity that participate in the disturbance of microcirculation found in non-arteritic RAO and AION.[10 25 26] Hence improving the blood fluidity by different treatment modalities (for example isovolaemic haemodilution,[29-31] fibrinogen depletion, pentoxyfylline) may well have a beneficial effect on the visual outcome of these diseases and should be tested by randomised prospective studies.

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Coexistent corneal disease and glaucoma managed by either drainage surgery and subsequent keratoplasty or combined drainage surgery and penetrating keratoplasty

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Abstract

The results of penetrating keratoplasty following trabeculectomy in 26 eyes where there was coexistent corneal disease and glaucoma are presented. Patients were aged 16–80 years at the time of drainage surgery (mean=51 years) and there was a mean of 33·5 months between trabeculectomy and keratoplasty. The mean pressure fell from 35·3 mm Hg prior to trabeculectomy to 14·9 mm Hg at the time of keratoplasty and 20 mm Hg 12 months after keratoplasty. There was a 0·45 probability of maintaining normal intraocular pressure with medication at 5 years after keratoplasty; and a similar graft survival probability. The probability of maintaining both a clear graft and a normal pressure was only 0·27 at 5 years. In another 22 eyes combined trabeculectomy and penetrating keratoplasty was performed. Patients' ages ranged from 21–82 years (mean 55) at surgery, and 73% were aphakic. The intraocular pressure dropped from a mean of 28·9 mm Hg preoperatively to 14 mm Hg at 12 months. There was a 5 year probability of 0·7 of maintaining a clear graft but if both a clear graft and normal intraocular pressure are considered then the probability falls to 0·5 at 5 years. The hazard ratio for intraocular pressure control and graft survival between the two groups suggests that combined surgery may offer a better prognosis.

The combination of raised intraocular pressure (IOP) and corneal opacification presents ophthalmologists with difficult management decisions. The association is not necessarily uncommon since bullous keratopathy may often be seen in association with aphakic or pseudophakic glaucoma.[1-16] Indeed the trauma of the initial cataract surgery may be a common aetiological factor.

In the situation where the corneal disease leads to permanent corneal scarring or opacification then visual rehabilitation by penetrating keratoplasty may be hampered by the worsening of the glaucoma even rendering medical control impossible. In other circumstances corneal opacification may develop following planned trabeculectomy rendering keratoplasty necessary if the patient is to achieve useful vision. Kirkness and Moshegov[17] pointed out that control of IOP usually deteriorated after keratoplasty in glaucomatous eyes but they did demonstrate that in some eyes the control surprisingly improved at least temporarily.

Opinions on the management of eyes with glaucoma and corneal disease have varied from the suggestion that penetrating keratoplasty is contraindicated[18] to the advice that penetrating keratoplasty may be undertaken once the IOP has been controlled surgically.[19] The trauma of graft surgery and the associated inflammation may however predispose to bleb fibrosis and failure so prejudicing control of IOP.

Despite the longstanding recognition of this problem, there is little substantive work published to support these anecdotal assertions. Since sequential surgery may not always be desirable and since it had at the time of commencement of this study an unproved prognosis there appeared to be a place for a combined procedure for penetrating keratoplasty and trabeculectomy. Combined cataract surgery and trabeculectomy, for instance, have an established a good prognosis with relatively low rates of complications.[20] The surgery involved in keratoplasty is more complex than cataract surgery and the results of combined procedures might well be expected to be worse as well as having more important complications. There is little information on combined keratoplasty and trabeculectomy apart from Insler *et al*[21] who reported seven cases with short follow-up but encouraging results. Barraquer *et al*[22] reported anecdotally similar encouraging results in a small number of patients.

More advanced cases of glaucoma which have already undergone trabeculectomy and failed or in which there is extensive anterior segment disorganisation and conjunctival scarring may be considered more suitable for insertion of silicone drainage tubing.[23]

The results from within the corneal clinic of Moorfields Eye Hospital, both from sequential surgery and from combined penetrating keratoplasty and glaucoma procedures, are presented in an effort to establish the likely success of the procedures from the point of view of graft survival, control of IOP, and visual acuity and also to try to establish the likely important complications of the surgery.

Field testing in this group of patients with corneal scarring and possibly additional cataract or aphakia is notoriously unreliable and changes in scotomata are often difficult to interpret. As a result rather more emphasis must sometimes be placed on the IOP than might be considered ideal. It must be stressed that these two series do not represent any attempt at randomisation. The surgery in each case was performed because it was deemed more appropriate by the surgeon in

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charge. As such there will inevitably be bias. Comparisons between the two groups must be interpreted with caution.

Patients and methods

Patients were identified from case notes and a database of patients attending the Corneal Clinic, Moorfields Eye Hospital. Since 1987 this work has been prospective but data acquired before this time were entered retrospectively from the case notes.

From 1975 to 1989 26 patients (26 eyes) were identified undergoing drainage surgery followed by keratoplasty – group A. No case was bilateral. Only cases in which keratoplasty was performed following drainage surgery were included. Eyes undergoing keratoplasty after drainage surgery where the drainage procedure had already failed at the time of keratoplasty were excluded from the study as were eyes which had already had combined drainage procedures and keratoplasty, that is any case of post-keratoplasty glaucoma was excluded.

In 24 cases there was a trabeculectomy and two eyes had silicone drainage tubes inserted for control of IOP. The mean follow-up was 94 months (SEM 19·7 – that is ±2 standard errors of the mean) and the mean interval between drainage and keratoplasty was 33·5 months (SEM 10·7). There is a minimum follow-up of 6 months on each patient following keratoplasty (in fact all have been followed for more than 12 months). Patients were aged from 6–80 years at the time of drainage, mean 51·3 (SEM 7·22), median 52.

Twenty two patients underwent combined drainage surgery and keratoplasty – group B. Patients' ages ranged from 21–82 years at the time of surgery, mean 54·8 (SEM 8·4), median 62. Follow-up is from 6 months to 8 years, mean 34 (SEM 11·5) months. All eyes had glaucoma, with poorly controlled raised IOP at the time of combined surgery.

The indications for keratoplasty in group A are shown in Fig 1. In group A two patients had a primary glaucoma leading to corneal endothelial failure. Anterior chamber cleavage syndromes also figure largely ($n=5$) but otherwise the disease categories reflect a spectrum of the usual groups at risk of developing post-keratoplasty glaucoma.

The indications for trabeculectomy in both groups were failure to control IOP adequately or to prevent field loss on (tolerable) medical therapy. Silicone drainage tube surgery was indicated where there had been a failure of conventional trabeculectomy to control IOP. Control of IOP was judged successful if the IOP was less than 21 mm Hg and partially successful if additional medical therapy was necessary to control the IOP; failure was surmised when it was not controlled below 21 mm Hg on maximum tolerable medication. If there was obvious progression of field loss or disc cupping, despite normal IOP, this was also considered to be failure.

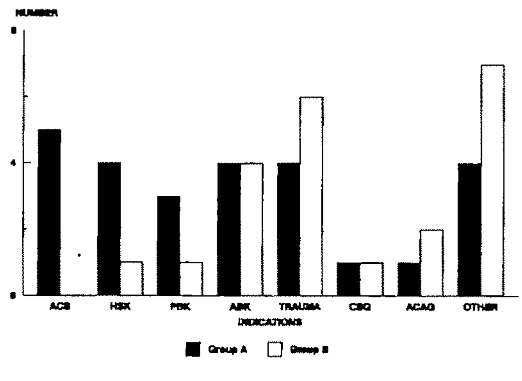

Figure 1 The indications for keratoplasty for patients in groups A and B. ACS= anterior chamber cleavage syndrome; HSK=herpes simplex keratitis; PBK= pseudophakic bullous keratopathy; ABK= aphakic bullous keratopathy; CSG=chronic simple glaucoma; ACAG= acute closed angle glaucoma.

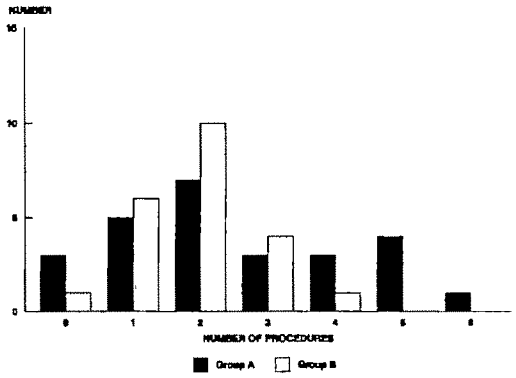

Figure 2 The number of previous intraocular procedures prior to drainage surgery, in group A (■) and prior to combined keratoplasty and drainage surgery in group B (□).

Eight of the 26 eyes in group A had undergone previous glaucoma surgery, with eight drainage procedures. Three of these eyes had undergone both trabeculectomy and cyclocryotherapy. Six eyes had had more than one procedure. The mean number of intraocular procedures of any type, was 2·6 (SEM 0·7) (Fig 2). In addition to glaucoma surgery a number of the eyes had had cataract surgery; 10 had had intracapsular extraction, including three with intraocular lens implant; two had had extracapsular extraction and one had had cataract surgery between trabeculectomy and keratoplasty. Fifteen of the eyes were phakic at the time of trabeculectomy and the remainder had had a variety of cataract procedures as shown in Fig 3. Although 14 eyes were phakic at the time of keratoplasty, only five remained phakic throughout the study. Eight had combined cataract extraction and keratoplasty and a further one had cataract surgery following keratoplasty.

The indications for penetrating keratoplasty in group B were also varied (Fig 1). Most eyes in group B had suffered anterior segment disorganisation from cataract surgery, trauma, or

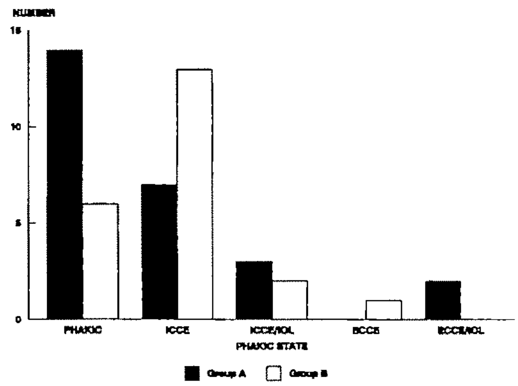

Figure 3 The phakic state at the time of keratoplasty for groups A and B. (ICCE=intracapsular cataract extraction, IOL=intraocular lens; ECCE=extracapsular cataract extraction.)

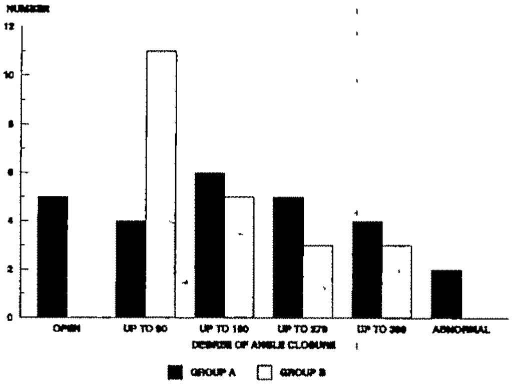

Figure 4 The amounts of synechial angle closure seen in groups A and B. (ICCE = intracapsular cataract extraction; IOL = intraocular lens; ECCE = extracapsular cataract extraction.)

corneal perforation but in four the glaucoma was secondary to inflammatory conditions such as herpes simplex keratitis or interstitial keratitis. Only one eye had had no previous surgery while the rest had from one to four previous intraocular procedures, mean 1·9 (SEM 0·4), prior to this surgery. Six eyes were still phakic at the time of surgery, 13 had had intracapsular cataract extraction, and the rest had had an extracapsular extraction (Fig 3). Seven of the 22 eyes in group B had had previous drainage procedures, all trabeculectomies, but in one eye a cyclodialysis had been performed in addition.

Full and accurate documentation of the angle is often difficult in these eyes and assessment after keratoplasty may be misleading. An attempt was made to estimate angle closure by quadrants retrospectively. In group A some degree of angle closure by anterior synechiae was present in 70% and 12% had complete angle closure; while in group B in two eyes the angle was completely and widely open; in one it was not possible to assess the angle owing to the degree of corneal opacification; in all others there was some degree of peripheral anterior synechiae ranging from occlusion in one quadrant to total angle obliteration (Fig 4).

All of the eyes might have been considered to have had relatively abnormal or scarred conjunctiva. Scarring was attributable to previous surgery which involved the conjunctiva or to ocular surface disease.

None of the patients were on long term topical steroid therapy.

Eleven of the eyes in group A required some medication to control IOP between the trabeculectomy and the keratoplasty.

THE SURGICAL TECHNIQUE – FOR COMBINED PROCEDURE

Prior to the keratoplasty a standard trabeculectomy was begun with either a limbus or a fornix based flap. A scleral flap was raised and the block for excision marked. The procedure was halted at this stage.

A standard penetrating keratoplasty was then performed with anterior vitrectomy, removal of implant, etc being performed as necessary. Once this was complete and the wound assured to be watertight the scleral block was excised and the trabeculectomy completed in the usual fashion with 10/0 nylon to the scleral flap and 8/0 virgin silk to the conjunctiva.

Survival probabilities and hazard ratios were calculated according to the methods of Machin and Gardner.[24]

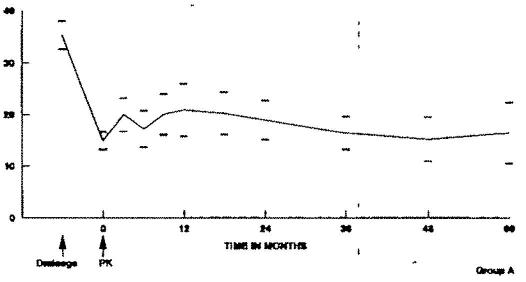

Figure 5A Group A: the mean intraocular pressures with time; means are shown (SD 95% confidence interval). Note the discontinuity of scale between drainage surgery and keratoplasty.

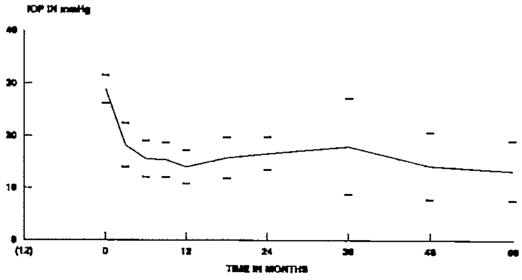

Figure 5B Group B: the mean intraocular pressures with time, means are shown (SD 95% confidence interval).

Results

GROUP A

The mean IOP fell from 35·3 (SEM 2·6) mm Hg prior to trabeculectomy to 14·9 (SEM 1·6) mm Hg at the time of keratoplasty. These results and the subsequent mean IOPs are shown in Fig 5A; this includes those of patients taking additional antiglaucoma medication where necessary. (Once a further drainage procedure was undertaken to control IOP in an eye, the IOP is no longer considered in this review.)

The IOP failed to be controlled without medication from within 1 week of keratoplasty to 45 months (50% in under 9 months) and with additional antiglaucoma medication from 10 days to 6 years. The survival probability had fallen to 0·5 between 32 and 45 months. The survival curves for these parameters are shown in Figs 6 and 7.

At the time of this review 12 eyes had failed to have adequately controlled IOP, six are controlled with additional medical therapy and eight are successfully controlled with no antiglaucoma therapy. The amount of antiglaucoma medication required after keratoplasty is shown in Fig

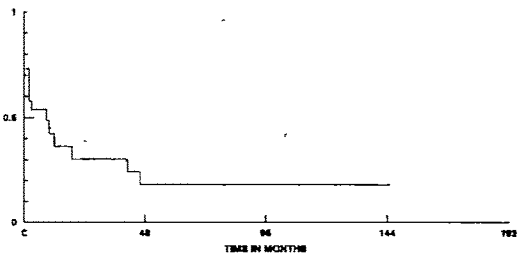

Figure 6 Probability of maintenance of normal pressure (up to 21 mm Hg) without additional antiglaucoma medical therapy, group A (—; n=26) and group B (—; n=22). Times taken from time of keratoplasty.

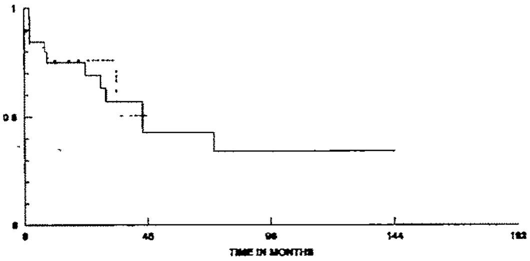

Figure 7 Probability of maintenance of normal pressure (up to 21 mm Hg) with additional antiglaucoma medical therapy where necessary, group A (—; n=26) and group B (---; n=22). Times taken from time of keratoplasty

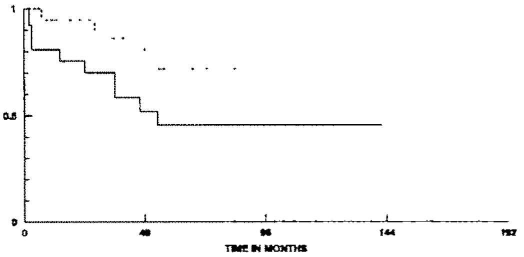

Figure 9 The probability of graft survival, group A (—; n=26) and group B (---; n=22). Times taken from time of keratoplasty

8. It may be seen that five patients are taking more medication after keratoplasty than they were taking before and it might be speculated that these eyes are also likely to fail to be controlled in due course. The range of antiglaucoma medications used reflects nearly all commonly available medications but carbonic anhydrase inhibitors, beta blockers, and pilocarpine were the most widely used.

Where control of IOP was lost, two eyes did not undergo further surgery since the visual function was so poor, five eyes underwent further trabeculectomy, two eyes had silicone tubes inserted, and three had cyclocryotherapy. Two of the trabeculectomies failed. One had a tube inserted which maintains successful control at the time of this review, and in the other eye subsequent cyclocryotherapy failed. One of the eyes receiving cyclocryotherapy had a tube inserted but this eye developed prolonged hypotony and is phthisical. Thus of the original 12 failures six are currently controlled following further procedure(s).

Failure of IOP control occurred in seven of the eight patients who had undergone previous procedures for control of IOP. Repeat trabeculectomy being followed by keratoplasty must be considered to carry a significantly worse prognosis – relative risk of failure 3·2, 95% confidence interval 1·4–6·9, compared with single trabeculectomy and keratoplasty.

Graft survival is shown in Fig 9. The survival of grafts in this group of patients is clearly poor with 50% failing at about 4 years. The causes of graft failure were rejections (n=7), recurrence of herpes keratitis (n=2), and recurrence of epithelial downgrowth (n=1). One graft each failed after retinal detachment and application of cyclocryotherapy.

The maintenance of both a clear graft and controlled IOP is (obviously) also poor but in fact closely parallels both previously described graphs suggesting that graft failure and loss of IOP control are in fact related (Fig 10).

Complications directly related to the surgery were seen infrequently. Three eyes had cystoid macular oedema which probably related to previous cataract surgery. One developed a retinal detachment following intracapsular extraction which had preceded keratoplasty. One eye developed microbial keratitis in the graft and one eye which had a tube in situ developed persistent hypotony after keratoplasty necessitating removal of the tube. This eye had already suffered graft failure from rejection.

The visual results are shown in Fig 11A. In many cases the visual potential was already reduced because of the preceding glaucoma, amblyopia, or other ocular disease. In seven eyes failure to control the IOP adequately remained the major cause of visual loss in the post-keratoplasty period. In five others vision was lost as a result of cyclocryotherapy, retinal detachment, epithelial downgrowth, diabetic retinopathy, and recurrence of herpes simplex keratitis, respectively. No relationship could be demonstrated between the outcome and the degree of peripheral anterior synechiae, lens state, or interval between drainage and keratoplasty.

GROUP B

The mean IOP preoperatively was 28·9 (SEM 3·5) mm Hg. This fell to 18·2 (SEM 4) mm Hg at 3 months and 15·6 (SEM 3·2) mm Hg at 6 months (Fig 5B).

At the time of this review, eight eyes are controlled successfully without additional medical therapy and a further seven with additional therapy. The survival curves for pressure control are shown in Figs 6 and 7. From these it can be seen that 50% are anticipated to require medical therapy within 6 months and 50% have failed completely by 3 years. Two eyes went on to have further trabeculectomy which failed and then silicone drainage tubes were inserted; two went on to have silicone drainage

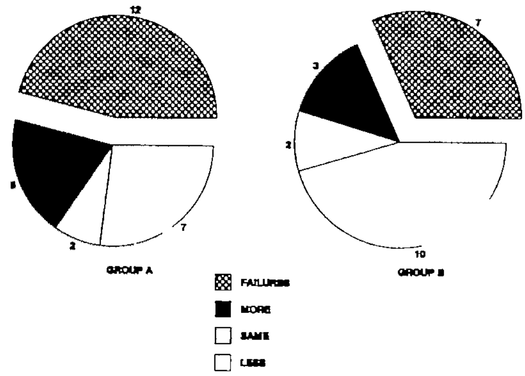

Figure 8 The need for additional medical antiglaucoma therapy, groups A and B

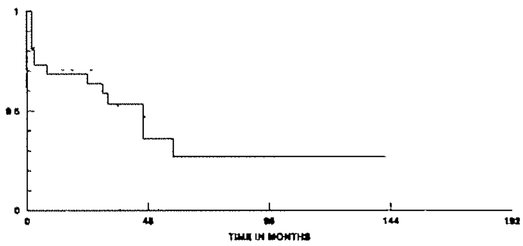

Figure 10 Probability of maintenance of normal pressure with additional antiglaucoma medical therapy where necessary and a clear graft, group A (—; n=26) and group B (---; n=22) Times taken from time of keratoplasty Normal IOP up to 21 mm Hg (with additional medical therapy where necessary).

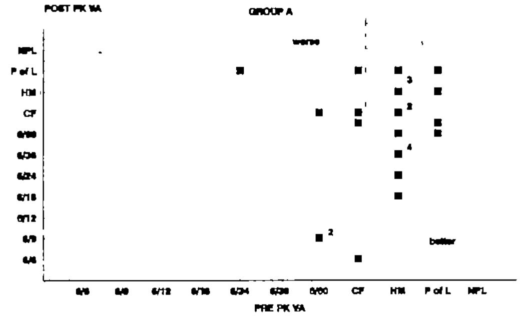

Figure 11A Group A: the change in acuity from before keratoplasty to the best refracted acuity afterwards.

tubes inserted and one had cyclocryotherapy. The distribution of medication and failures is shown in Fig 8. Patients undergoing a repeat trabeculectomy as part of the combined procedure did not have a greater risk of failure of control of pressure, relative risk 0·86, 95% confidence interval 0·22 to 3·4.

Complications directly attributable to the surgery were rare but one eye with a history of herpes simplex keratitis which underwent, in addition, an extracapsular lens extraction had a flat anterior chamber immediately postoperatively lasting several days. When the chamber reformed spontaneously approximately 120° of anterior synechiae to the graft-host interface were found. No action was taken and this graft survives with well-controlled IOP and good vision 4 years later. Graft survival was moderate with a probability of survival of 0·7 at 5 years. When the maintenance of a both clear graft and normal IOP is considered the survival probability is 0·5 at 3 years (Figs 9 and 10).

Only one eye lost vision compared to preoperative levels, six remained the same and the remainder improved by variable amounts (see Fig 11B). As well as continuing optic disc damage and lack of graft clarity causing visual loss there was one instance each of cystoid macular oedema, age-related macular degeneration, retinal detachment, and optic disc ischaemia thought to be independent of the glaucoma. There was also one case of late hypotony which resulted in poor vision. All grafts which failed did so following rejection episodes.

Although not randomised the two groups may be compared statistically. The hazard ratio for maintenance of IOP control (with additional medication where necessary) at 5 years for combined versus sequential surgery is 0·40, 95% confidence interval 0·15 to 0·90. This strongly suggests that sequential surgery is less successful in maintaining IOP control. Similarly the hazard ratio for maintenance of graft clarity at 5 years is 0·4, 95% confidence interval 0·14 to 0·95. This too suggests that there is some advantage in the combined procedure.

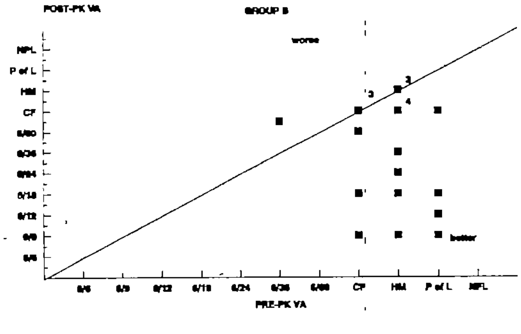

Figure 11B Group B: the change in acuity from before keratoplasty to the best refracted acuity afterwards.

Discussion

The coexistence of glaucoma and corneal disease can result in severe limitation of vision. The accepted approach for visual rehabilitation recommends controlling the pressure before proceeding to keratoplasty. Until the present study no data existed as to the likely outcome of such an approach. Eyes with this combination of disease represent a serious challenge to both surgeon and patient alike. The success of this surgery needs to be assessed in three main areas, namely intraocular pressure control, graft clarity, and recovery of visual acuity.

INTRAOCULAR PRESSURE

One of the most important determinants of success of drainage surgery is the degree of fibrosis which develops in the bleb. Hitchings and coworkers have clearly established that prolonged topical antiglaucoma therapy may have a deleterious effect on bleb formation by enhancing conjunctival fibrosis.[25] They also showed that eyes in which there is established conjunctival scarring are also recognised as having a reduced prognosis for successful IOP control.[26 27] Cataract extraction through a standard limbal approach inevitably leads to conjunctival scarring. On this basis all the eyes in this series might be considered as being poor risks for filtration surgery since they had been on long term topical therapy, had scarring from previous ocular surgery, or ocular surface disease. This is further substantiated by the fact that several of the eyes required additional antiglaucoma medication by the time keratoplasty was undertaken in group A in a mean of under 3 years. Conjunctival scarring is probably the most potent reason for poor pressure control in both groups in this series.

Most of the surgery described here predated the experimental use of 5-fluorouracil to reduce bleb fibrosis. Its use however in non-grafted patients indicates that loss of corneal epithelium is an important side effect.[28] Such an occurrence could have serious implications for graft survival and to our knowledge no series has been reported using this drug in the presence of corneal grafts.

Gross *et al*[29] showed that the aphakic eye per se may also have a reduced prognosis for IOP control. Earlier Bellows and Johnston[30] presented data from trabeculectomy for glaucoma in aphakia from which it is possible to derive survival curves. These indicate a survival proportion for the maintenance of IOP control at 5 years of 37%. This is very similar to the present data in both groups.

In group A the major factor common to most failures was a repeat trabeculectomy. Seven out of eight eyes which had had repeat trabeculectomy failed compared with only five out of 18 in which there was only one drainage procedure, a difference which appears highly relevant with a relative risk of 3·2 and 95% confidence of 1·4–6·9. These data would suggest that should a trabeculectomy have failed in the presence of corneal disease, repeat trabeculectomy is unlikely to control the IOP when a corneal graft is undertaken. Silicone drainage tubing may offer a better prospect of success. Kirkness *et al*[23 31] and McDonnell *et al*[32] have shown encouraging results for the control of glaucoma associated with keratoplasty by the use of silicone drainage tubing of various designs. In group B it is curious however that repeat trabeculectomy combined with keratoplasty did not appear to have an adverse prognosis.

It is difficult to explain why the keratoplasty should be associated with deterioration of IOP control but several suggestions can be made. The increased inflammation developing following surgery in these eyes (which have had a mean of 2·6 previous intraocular procedures) might predispose to both increased bleb fibrosis and the development of peripheral anterior synechiae.

The mechanisms involved in the development of post-keratoplasty glaucoma may be relevant to the mechanisms of loss of IOP control in both groups A and B. Olson and Kaufman[7] have suggested that the combination of aphakia and keratoplasty allows trabecular collapse which reduces outflow. Much of the mathematical background of this work depends upon graft host bed disparity. All the surgeons involved in the present series pay particular attention to graft sizing and all of the donor buttons used were measured to be at least as big if not bigger than host bed. Nevertheless the possibility of trabecular collapse as one component cannot be ruled out entirely. While there has been considerable discussion as to the mechanisms involved in the development of post-keratoplasty glaucoma there is only a little support for the view that at least part of the problem relates to the formation of fine peripheral anterior synechiae closing the angle[33] which is neither widely reported nor well documented in most series. The patients in this study are a closely related group. Many already had extensive peripheral anterior synechiae. Since peripheral anterior synechiae were so common it was not possible to highlight it as an additional risk factor for loss of IOP control but it is clearly a strong association for these forms of secondary glaucoma. Because of the difficulty in assessing peripheral anterior synechiae through opaque corneas it is also not possible to comment on whether peripheral anterior synechiae tended to increase following keratoplasty predisposing to loss of IOP control.

GRAFT SURVIVAL

The survival of corneal grafts is slightly better in group B than those in the series reported by Gilvarry *et al*[34] where glaucoma becoming uncontrolled after keratoplasty was managed by trabeculectomy. Gilvarry's series did however contain a higher proportion of repeat keratoplasties which are known to have a poorer prognosis. The nature of eye disease was similar in both series – as might be expected since the common aetiological factors for the development of post-keratoplasty glaucoma are well recognised. The survival of grafts in group B is similar to graft survival in aphakic bullous keratopathy in general[35] and reflects the most common indication for keratoplasty in the group.

The survival of grafts in group A was very similar to Gilvarry's series. Also similar to Gilvarry *et al* was the high proportion in both groups A and B failing to be controlled by drainage surgery alone and the need for additional anti-glaucoma medication. In both groups the addition of medication was sufficient to control IOP in the majority of cases. Those failing and requiring further drainage surgery – trabeculectomy or silicone drainage surgery did so relatively soon after following graft surgery.

VISUAL ACUITY

Visual improvement was similar between both groups. Approximately 15% obtained a corrected acuity of 6/12 or better, and two thirds in both groups showed visual improvement of at least one line of Snellen acuity. The reasons for poor acuity were often multifactorial although the presence of pre-existing glaucoma was often pertinent. These eyes do present complex problems and recovery of normal vision would not be expected in many.

Summary

The majority of eyes in the two groups reported have the common feature of anterior segment disorganisation involving particularly the cornea and drainage angle. They also appear to behave in a similar fashion to eyes which develop post-keratoplasty glaucoma and have many physical findings in common.

The disappointing results for both pressure control and graft survival when viewed in conjunction with the additional complications suggest that drainage surgery followed by penetrating keratoplasty may not be an ideal way to manage combined corneal disease and glaucoma. Where the vision is good in the fellow eye careful patient selection may limit the extent of the problem but individual cases will remain at risk. Comparison with group A indicates that combined drainage surgery and keratoplasty offers a better management option for patients with coexisting glaucoma and corneal disease. The combined approach also offers a quicker visual rehabilitation.

Where keratoplasty is deemed worthwhile consideration should be given to either a combined approach of trabeculectomy and keratoplasty or to the use of silicone drainage tubing where there is obvious conjunctival disorganisation. It is self evident that both surgeon and patient should understand the prognosis when embarking on such surgery.

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Neuroleptanalgesia and extracapsular cataract extraction

P R Hodgkins, L Teye-Botchway, A J Morrell, T J Fetherston, C Perthen, N E Brown

Abstract

Peribulbar and retrobulbar anaesthesia are commonly used techniques in cataract extraction. They offer satisfactory analgesia and akinesia but serious complications although uncommon are consistently reported. Intravenous sedation combined with a facial nerve block offers an alternative method of anaesthesia. This is a retrospective study of patients who underwent extracapsular cataract extraction using this technique between 1 January 1986 and 1 September 1990. The operating conditions were judged to be very suitable with minimal peroperative complications. The postoperative ocular complication rate was low (minimum follow-up 3 months) and no serious medical complications were noted: 93·8% of patients achieved 6/12 vision or better. This study demonstrates that it is possible to achieve satisfactory ocular analgesia and akinesia during cataract extraction under local anaesthesia without the use of a periocular injection.

It has been reported that comparable ocular akinesia and analgesia are achieved using retrobulbar one-site periocular injection[1] or superior bulbar subconjunctival bupivacaine and hyaluronidase.[2] Other authors[3] have reported retrobulbar and facial nerve block as a satisfactory technique for local anaesthesia.

Retrobulbar block for cataract surgery although relatively safe has infrequent but serious complications which have been consistently reported. These include intradural or subarachnoid injection;[4] retrobulbar haematoma in 1–3% of cases;[5] central retinal artery or vein occlusion;[6] optic nerve contusion and atrophy;[7] perforation of the globe;[8] and rarely life-threatening apnoea.[9]

Despite these risks absolute ocular akinesia is not guaranteed. Peribulbar anaesthesia using a shorter needle outside the muscle cone was suggested to eliminate some of the complications while providing similar akinesia and analgesia.[10] It does not eliminate the risk of globe perforation[11] although a series of 6000 cases has been reported in which no scleral perforation occurred.[12]

We describe our experience using an alternative method of local anaesthesia without periocular injection.

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Patients and methods

A retrospective review of the case notes was carried out on all patients who underwent a planned extracapsular cataract extraction with implant under local anaesthesia in the South Warwickshire District between 1 January 1986 to 1 September 1990. Those patients who underwent a combined procedure were excluded from the study.

LOCAL ANAESTHETIC TECHNIQUE

Preoperatively all patients had a full history and examination by an ophthalmic senior house officer and were subsequently assessed by the anaesthetist. Patients over 60 had a full blood count. A sickle cell test was performed on patients of African or West Indian origin. The urea and electrolytes were measured in patients on antihypertensives or diuretics. Patients over 50 years of age or those with cardiovascular disease had an ECG, and a chest *x* ray was taken in those with respiratory or cardiovascular disease or a history of smoking. A cervical spine *x* ray was also taken if clinically indicated to anticipate any problems if intubation were to be required. Patients were assessed for their ability to lie supine for 30 minutes with physiotherapy, nebulisers, and short dose steroids used where necessary to achieve this.

The majority of patients were elderly often with one or more associated diseases giving them an American Society of Anesthetists grading of 2–5.

For patient awareness and acceptance the anaesthetic technique was fully explained by the surgeon prior to the day of surgery and then again by the anaesthetist. This helped to maximise patient understanding and cooperation whilst minimising the intraoperative sedation required.

Approximately 45 minutes preoperatively 0·75–2·0 ml of Thalamonal (50 mg fentanyl and 2·5 mg droperidol per ml) was administered intramuscularly according to size. In the anaesthetic room 5 ml of 2% lignocaine were injected as a facial nerve block and amethocaine drops applied to the eye. During the operation supplementary Thalamonal and midazolam were administered by the anaesthetist who remained present at all times. Topical amethocaine was applied if necessary. Supplementary oxygen was given by a tube adjacent to the mouth and continuous monitoring of the ECG, oxygen saturation, blood pressure, and respiration was performed.

At the end of the procedure the patient would usually be sufficiently alert to return directly to the ward.

CATARACT EXTRACTION

Using the operating microscope a superior rectus suture was positioned. A corneal or limbal incision was performed followed by a non-automated extracapsular cataract extraction without iridotomy. Sodium hyaluronate 1% or methylcellulose 2% was used to protect the corneal endothelium, maintain the anterior chamber, and open the capsular bag during insertion of the posterior chamber intraocular lens. The colloid was aspirated after wound closure and replaced with saline. Primary posterior capsulotomy was not performed.

Results

During the stipulated period 2026 patients underwent cataract surgery. The case notes were available for 1858 cases. A minimum period of 3 months documented follow-up was specified which eliminated 41 patients leaving 1817 for further analysis; 10% of patients were therefore unavailable for follow-up and this must be considered in the interpretation of the results. The average period of follow-up for which notes were available was 12·7 months with a maximum of 53 and a minimum of 3 months; 1173 (65%) of the patients were female. The age of the group ranged from 33 to 102 years with an average of 73·2 years (see Table 1).

The preoperative corrected visual acuity was 6/24 or less in 76% of patients (see Table 2). A subgroup of 24% of patients had vision of 6/18 or better – all had focal posterior cataracts or advancing nuclear sclerosis producing a significant visual handicap. Following surgery the corrected visual acuity of these patients improved to 6/12 or better in 93·8% of cases. Of those patients achieving less than 6/18 vision 102 patients were noted to have pre-existing ocular conditions unrelated to the surgery contributing to their poor visual outcome (see Table 3). In six patients poor visual outcome was secondary to complications related to surgery – one case of endophthalmitis, one choroidal haemorrhage, four patients with refractive errors. In three patients no reason for the reduced visual acuity had been recorded in the notes.

Table 1 Age and sex distribution of patients

	Female	*Male*	*Total*
Number of cases	1173	644	1817
Mean age (years)	74 7	70·4	73 2
Age range (years)	33–102	42–93	33–102

Table 2 Pre- and postoperative corrected visual acuity

	>6/6	*6/9–6/18*	*6/24–6/60*	*<6/60*
Pre	0%	24·3%	58 6%	17·1%
Post	12·8%	82 9%	3·8%	0·5%

Table 3 Aetiology of cases with a final visual acuity <6/18

	No of eyes
Pre-existing ocular conditions	
Diabetic retinopathy	13
Age-related macular degeneration	33
Myopia	31
Glaucoma	12
Amblyopia	5
Previous retinal detachment repair	5
Complications following surgery	
Choroidal haemorrhage	1
Endophthalmitis	1
Vein occlusion	1
Refractive error	4
No diagnosis recorded	3

Table 4 Complications associated with surgery in 1817 eyes

	No of eyes
Intraoperative	
Expulsive choroidal haemorrhage	1
Posterior capsule rupture with vitreous loss requiring an anterior chamber lens	31
Immediate postoperative	
Endophthalmitis	3
Iris prolapse	11
Residual soft lens matter	43
Residual soft lens matter requiring secondary washout	4
Long-term postoperative	
Retinal detachment	3
Cystoid macular oedema	5
Posterior capsule thickening requiring Nd:YAG laser capsulotomy	278

COMPLICATIONS

Intraoperative complications (see Table 4)

These included 31 cases of posterior capsule rupture with vitreous loss necessitating an anterior chamber lens. Cases in which there was a small posterior capsule break without significant vitreous loss received a posterior chamber lens. All the patients in this study received a primary intraocular lens implant. Twenty two (71%) of the cases in which vitreous loss occurred were performed by a junior surgeon (SHO or clinical assistant). In one patient vitreous loss occurred when the patient made a large head movement as someone unexpectedly entered the theatre.

One expulsive haemorrhage occurred as the anterior chamber was entered. The patient had a normal preoperative intraocular pressure and was calm throughout the procedure allowing closure of the section without loss of intraocular contents.

Immediate postoperative complications

These included three cases of endophthalmitis of which two eventually achieved better than 6/18 vision, the third patient remaining at 6/36+2 following treatment with intensive topical and systemic antibiotics. Eleven cases presented with an iris prolapse 1 to 15 days following surgery. All had iris reposition and resuturing of the section performed successfully under local anaesthesia; 43 patients were noted to have residual soft lens matter and in four of these cases an anterior chamber washout was subsequently required. All cases of iris prolapse and residual lens matter subsequently achieved visions of 6/12 or better.

Long-term ocular complications

These included three cases of retinal detachment one of whom had vitreous loss at the time of surgery. All three patients had successful detachment surgery with two patients achieving a final visual acuity of 6/18 and the other 6/9. Five patients were noted to have cystoid macular oedema postoperatively, in each case rupture of the posterior capsule had occurred at the time of surgery. The diagnosis of macular oedema was made on clinical grounds – no patient in this survey was felt to require investigation with fundus fluorescein angiography. The onset occurred 1–4 months following surgery with a reduction in visual acuity from 6/12 (or better) to 6/36 (or worse). All five cases subsequently achieved visions of 6/18 or better: 278 eyes (15·3%) developed opacification of the posterior capsular sufficient to require a Nd:YAG laser capsulotomy.

Medical complications

These included 19 men with urinary retention requiring catheterisation (3% of the male patients, 1% of all patients), but no other serious medical sequelae were encountered. One adverse psychological effect of the sedation which has apparently been encountered in other applications of these drugs was a state of heightened anxiety coupled with an inability to express these fears. Patients' descriptions of this phenomenon were quite specific and we estimate the incidence as being less than 1%. This is by far the commonest cause of patient dissatisfaction with the technique.

No cases of significant respiratory depression were noted with this dose of fentanyl. No patient in this series required intubation and no case needed transfer to either a medical ward of ITU postoperatively. The occasional patient in whom the oxygen saturation fell below 90% was relieved by the anaesthetist supporting the jaw – the surgeon being able to continue without interruption and with no apparent delay in the patient's recovery.

Discussion

In this study cataract surgery was performed under intravenous sedation combined with a facial nerve block and topical anaesthesia. Ocular akinesia and anaesthesia were judged by the surgeon to be very suitable for operating without the inherent risks and unpleasantness of a periocular injection. The anticipated difficulties due to excessive eye movement did not materialise. Any residual movement was slight and in the horizontal plane so the surgeon was easily able to compensate for it. One patient sustained a posterior capsule rupture with vitreous loss after making a large head movement when he was startled by someone entering the theatre. Head movements are a risk in all cases performed under local anaesthesia[13] including retrobulbar anaesthesia. We believe however that there is a lower incidence of such problems when intravenous sedation is used.

The combination of droperidol and fentanyl induces a state of 'neuroleptanalgesia' with the emetic effect of fentanyl a powerful analgesic being offset by the anti-emetic effect of the tranquilliser droperidol. There is a relative insensitivity to pain and the patients stay motionless quite indifferent to their surroundings. Nevertheless they retain consciousness and respond to commands (albeit a little sluggishly).

It became clear to us that with adequate topical anaesthesia a cataract procedure is not in essence a painful procedure. The sedation does not render the patient unable to respond to pain – if a painful procedure such as a peripheral iridectomy was carried out the patient would respond and express discomfort. Increasing the degree of sedation does not counter discomfort, but merely tends to produce patient confusion and detracts from the patient's ability to comply with commands.

There was a very low incidence of medical complications even in this elderly age group, with no major medical problems documented. The recovery period was rapid without nausea and the majority of patients were able to drink within 30 minutes of returning to the ward.

The 3% incidence of urinary retention among male patients compares with reports of 6% of patients developing urinary retention following general surgical procedures.[14] In the latter study it was noted that urinary retention was more common following opiate analgesia and it is possible that the use of fentanyl for neuroleptanalgesia may contribute to the problem of urinary retention either by causing a diminished awareness of bladder sensation or by reducing parasympathetic tone in the bladder.

In our department unless a relief anaesthetist is present who is unfamiliar with the technique a general anaesthetic is given for the following indications: mental subnormality; language difficulties; extreme agitation; age less than 50; or a strong patient preference.

A satisfactory general anaesthetic does guarantee absolute ocular akinesia and usually allows the eye to be kept soft. It has been reported that there is no difference in major morbidity or mortality when comparing general anaesthesia to regional anaesthesia in patients over 90 years old.[15] However a general anaesthetic does leave the patient more drowsy; diabetics often require an intravenous infusion and confusion is probably more common following a general anaesthetic in the elderly. Endotracheal intubation carries a small but significant risk of serious complications which are eliminated with the local anaesthesia/intravenous sedation technique.

There were drawbacks to the technique. The idiosyncratic psychological reactions – probably caused by droperidol – were unpleasant for a small minority of patients. In addition if the dose of Thalamonal is to be kept to a reasonable level this limits the length of the surgery and the technique is therefore less suitable for teaching inexperienced surgeons.

Despite these difficulties the results of surgery are comparable with those obtained using other techniques of anaesthesia. The visual outcome of cataract surgery with intraocular lens implantation in this series was 6/12 or better in 93·8% of cases. These figures compare favourably with results reported by other authors.[16–18] The low incidence of operative complications is also notable – the complication rate using local anaesthesia/intravenous sedation comparing favourably with other techniques of anaesthesia.[19–22]

The lack of medical problems and the speed of recovery make this technique an acceptable method of anaesthesia without retrobulbar injection possibly for use in day case surgery. Patients who had a general anaesthetic for the first eye (prior to the introduction of the technique) usually strongly preferred the local anaesthetic/intravenous sedation technique when this was used for the second eye.

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The importance of the precorneal tear film for the quality of optical imaging

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Abstract

The optical function of the eye critically depends on the presence of an intact precorneal tear film. Abnormalities of the tear film such as those occurring in the dry eye syndrome or in otherwise irritated eyes may interfere with vision. In 30 patients with dry eyes artificial tears were found to produce stastistically significant improvement of vision ($p<0{\cdot}001$) while no significant changes were seen in the untreated partner eyes. Static perimetry in another 30 patients using the 'macular programme' of the automatic Humphrey 620 perimeter showed artificial tears to increase mean thresholds significantly ($p<0{\cdot}001$) whereas no significant differences were seen in the untreated partner eyes.

With a refractive power of 49 dioptres the corneal surface is the highest refractive optical interface in the human eye.[1] However it needs continuous and homogeneous wetting for optimal quality of the optical image and function of the eye. Wetting is provided by the three layers of the precorneal tear film which guarantee a smooth and even surface. Thus the tear film is a 'polish' of the most important refractive medium – the cornea.[2]

Apart from preventing dryness and infection and protecting the transparency of the cornea by its hyperosmolarity the tear film is essential for ensuring an optimal optical function of the eyes. Like the cornea and the crystalline lens it is among the important optically relevant structures of the refractive media.[3] If unstable it impairs vision.[3]

Appreciable variations of visual acuity in patients with dry eyes and the reported occurrence of (pseudo) scotomas seen on perimetry[4] prompted us to investigate the effect of tear film stability on the quality of optical images and vision.

Material and methods

Thirty patients without ocular abnormalities (18 females, 12 males; worst vision 0·8) aged between 42 and 78 years (mean age 60·4 years) presenting with dry eyes were investigated. Dry eyes were diagnosed on the basis of subjective symptoms – 6 mm wetting or less in the Schirmer test in local anaesthesia (means 2·83 mm OD and 2·37 mm OS with test strips in OD first) and a break-up-time (BUT) of less than 10 s (mean 3·0 s). Under standardised conditions (DIN 58 220) optimally corrected vision was evaluated separately for the two eyes 1 day after the Schirmer test and the determination of the BUT. One drop of a 2% poly(vinylpyrrolidone) solution was applied to the right eye and vision was again tested 5 minutes later. Visual acuities before and after tear replacement were compared. Analyses were based on the difference in the number of correctly read optotypes. The untreated left eyes served as controls.

In another group of 30 patients with dry eyes (19 females, 11 males; worst vision, 0·8) aged between 43 and 76 years (mean age 61 years) perimetric thresholds were determined 1 day after keratoconjunctivitis sicca had been diagnosed. Using the 'macular programme' of the Humphrey 620 computerised perimeter data were first obtained for the right eye. After instilling artificial tears into the right eye thresholds were determined for the left eye. Then fields were again tested for both eyes with the right eye being examined first. Thresholds in dB – that is, means of three readings, were evaluated. The sum total of all 16 measuring points before tear replacement was compared with that after tear replacement. Statistical analysis was performed with Wilcoxon's matched pair test.[5] The untreated left eyes served as controls.

Results

In the group of patients with tear replacement in OD 25 of the 30 eyes (83%) showed improved visual acuity by 1 to 4 optotypes (mean +2·6 optotypes). In five eyes (17%) visual acuity was unchanged.

Of the 30 left eyes which served as untreated controls 17 (56%) showed no statistically significant improvement (1 to 4 optotypes (mean +1·6 optotypes)). Six eyes (20%) were unchanged. In seven eyes acuity had slightly deteriorated by 1 to 2 optotypes (mean −1·4 optotypes).

Statistical analysis using Wilcoxons's matched pair test showed a mean acuity gain of +2·33 optotypes after tear replacement. The difference was highly statistically significant (significance level 99·999%).

In the control group a mean gain of +0·54 optotypes was seen, but the difference was not statistically significant (significance level 92·313%) (Fig 1).

Macular thresholds determined by static computerised perimetry showed a similar pattern. Of the 30 patients with tear replacement in OD 20 (66·66%) were found to have gained between +1 and +39 dB (mean +11·75 dB), while 10 patients (33·3%) had lost between −1 and −18 dB (mean −8·3 dB).

In the untreated controls (30 left eyes) thresholds had increased by +1 to +17 dB (mean +6 dB) in 12 eyes (40%) while 18 eyes (60%) had lost between −2 and −17 dB (mean −7·77 dB).

Statistical analysis using Wilcoxon's matched pair test showed mean threshold gains of +0·31

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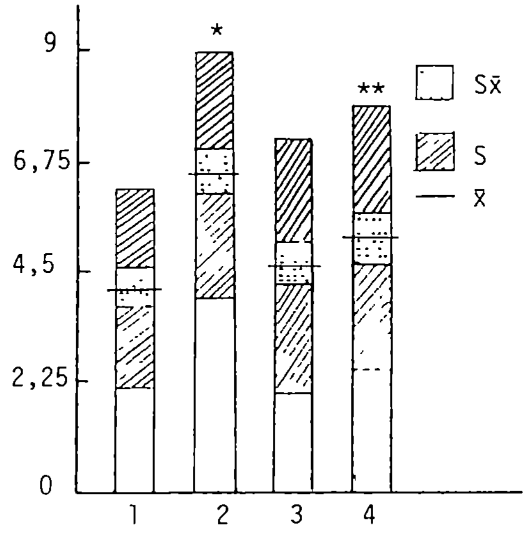

*Figure 1 Visual acuity examinations (number of correctly read optotypes of the obtained line of acuity) before (column 1) and after treatment with artificial tear fluid (column 2) and controls without artificial tear fluid (column 3, column 4: 5 minutes later). Statistical significance (Wilcoxon's paired test): *=9·999% and **92·813% compared with examination before rest* (n=*30*).

dB after tear replacement. The difference was again highly statistically significant (significance level 99·99%).

In the untreated controls mean thresholds had decreased by −0·11 dB. The difference was not statistically significant (significance level 94·54%) (Table 1).

Table 1 Wilcoxon's paired test of the differences (dB) between the first and the second test of the static computerised perimetry (macula programme)

	Difference (n)	*Mean*	*Significance level*
Right eye*	480	+0·31	>99·99%
Left eye*	480	−0·11	94·54%

*Right eye: treatment with artificial tear fluid
Left eye: without treatment.

Discussion

Our studies underscore the significance of an intact and stable precorneal tear film for the quality of optical images and for the optical function of the eye. In patients with dry eyes tear replacement apparently had a beneficial effect on the physical and chemical properties of the precorneal tear film and on the corneal surface. This was reflected in a statistically significant improvement of visual acuity and of threshold readings on static perimetry. The reduced threshold in visual field testing by itself does not prove that a poor tear film causes pseudoscotomas. However the improvement of threshold readings on static perimetry after instilling artificial tears may suggest this possibility. In patients with dry eyes undergoing examinations, that is perimetry as well as acuity tests, this should be allowed for. Focusing during examinations with fewer blinks but also a reduced blinking rate as seen while watching TV, reading, in screen-workers, etc further reduces the stability of the tear film in patients with dry eyes so that acuities and thresholds may appear worse than they actually are. Even in patients with normal tear function (including children!) but otherwise irritated eyes (contact lens wearers, in air-conditioned rooms, in airplanes, trains, etc) the stability of the tear film may be considerably disturbed. In patients with reduced tear film stability certain examinations such as acuity tests and perimetry should therefore be preceded by the instillation of artificial tears.

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The chemoattractant activity of the vitreous to human scleral fibroblasts following retinal detachment and proliferative vitreoretinopathy

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Abstract

The results are presented of a migration assay of scleral fibroblasts to 25% diluted vitreous samples from 27 patients with complex retinal detachments divided into three groups: group 1, no proliferative vitreoretinopathy (PVR); group 2, early PVR; and group 3, advanced PVR. There was a statistically significantly greater migration with vitreous samples from group 3 than with group 1 ($p<0\cdot0001$) but no significant correlation for migration with the age of patients, duration of retinal detachment, or number of retinal procedures undertaken. Analysis of vitreous by gel electrophoresis showed that cellular migration was proportional to the number of peptide bands. Vitreous fibronectin levels were measured and there was a positive correlation between fibronectin in the vitreous samples and the migration of fibroblasts to the vitreous ($r=0\cdot68$, $p<0\cdot004$).

Proliferative vitreoretinopathy (PVR) is a major cause of blindness, and is a common sequel to long standing rhegmatogenous retinal detachment surgery.[1-3] A critical component of the pathogenesis of PVR is the migration of cells that participate in the scarring process. Retinal pigment epithelial (RPE) cells have been implicated in this process as have macrophages and glial cells.[4-8] Fibroblasts are also present in the epiretinal membranes of proliferative vitreoretinopathy and may also have an important role in the evolution of PVR.[9 10]

It has been shown that the various cell types can produce a variety of extracellular matrix components such as collagen and fibronectin which contribute to the structure of scar tissue.[11-14] In addition epiretinal membrane cells and in particular RPE cells produce and possibly secrete into the surrounding media agents which stimulate the migration and proliferation of other cell types.[11 15 16]

Table 1 Clinical data for each of groups 1, 2, and 3

	Mean	*Range*
Group 1 ($n=12$) no PVR		
Age	36·3 years	16–71 years
No of operations	1 1	1–2
Duration of detachment	5·7 weeks	0·3–9 weeks
Group 2 ($n=3$) early PVR		
Age	51·6 years	36–76 years
No of operations	1·3	1–2
Duration of detachment	8·0 weeks	4–16 weeks
Group 3 ($n=12$) advanced PVR		
Age	45 5 years	22–73 years
No of operations	1 6	1–4
Duration of detachment	15 4 weeks	2–16 weeks

PVR=proliferative vitreoretinopathy

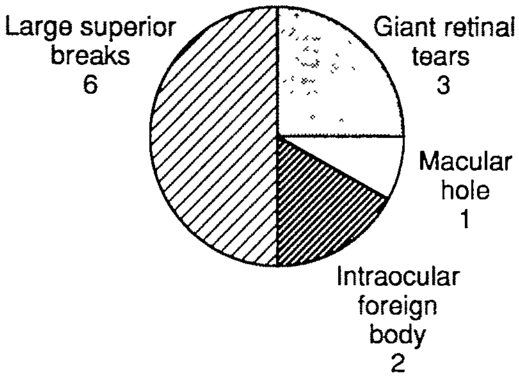

Figure 1 A pie chart of the aetiology of retinal detachment in group 1 patients.

The aim of the present study was to investigate the chemoattractant qualities of vitreous obtained from eyes with various types of complex retinal detachments and to determine whether this activity varied with clinical parameters. The target cells were cultured human scleral fibroblasts.

Materials and methods

Vitreous aspirates (0·5–1·0 ml) were obtained from 27 eyes in 27 patients undergoing vitrectomy for complex retinal detachments. These eyes, none of which had previously undergone vitrectomy, could be divided into three groups (Table 1): group 1 (12 eyes) no PVR (Fig 1); group 2 (three eyes) early PVR defined as vitreous haze and mild retinal wrinkling; group 3 (12 eyes) advanced PVR defined as fixed retinal folding involving one or more quadrants of the retina.

In all cases information about the age of the patient, the duration of retinal detachment, and the number of previous 'conventional' non-vitrectomy retinal detachment procedures was obtained at the time of surgery. The assays for migration and fibronectin were however performed without knowledge of this information.

PREPARATION OF VITREOUS

Aspirates of vitreous gel were obtained via the pars plana using a 1 ml syringe attached to the vitreous cutter by silicone rubber tubing. All samples of vitreous gel were obtained prior to the commencement of the pars plana infusion to prevent contamination by irrigation fluid and in no case was there contamination by admixed blood. A minimum volume of vitreous of at least 0·5 ml was obtained from all eyes.

Immediately after being obtained vitreous samples were stored at −70°C. Before use the vitreous was thawed, homogenised, and filter sterilised through a 0·22 μm filter (Millipore, USA).

CELL CULTURE

Human scleral fibroblasts (HSF) were grown from primary explants obtained from a single postmortem human eye (male aged 36 years) and with no known ophthalmic disease. They were grown in 25 cm² flasks (Sterilin UK) in minimal essential media (MEM) (Gibco UK) supplemented with 10% newborn calf serum (NCS, Gibco, UK) in 5% CO_2 at 37°C. They were passaged in a 1:3 ratio when they reached confluence.

MIGRATION ASSAY

HSF from the third to fifth passage were used in the migration assay. Forty-eight microwell chambers (Neuro Probe, Cabin John, MD, USA) were used with polycarbonate membranes coated with gelatin with pores 8 μm in diameter (Nucleopore, Pleasanton, CA, USA).

Confluent HSF were detached from their culture flasks by trypsin 0·25%/EDTA 0·02%. The enzymatic treatment was terminated by the addition of MEM containing 10% NCS. The cells were washed in serum-free MEM and counted in a Coulter counter. A volume of 50 μl of serum-free MEM containing 40 000 HSF was added to the upper chambers of the wells. Vitreous samples were diluted in serum-free MEM to produce a 25% solution, the concentration found from dose-response studies to produce the optimum chemotactic effect. Twenty-five μl aliquots of the diluted vitreous were added to the lower chambers of the 48-well apparatus and the lower chambers covered with the polycarbonate membrane.

The whole apparatus was incubated in 5% CO_2 at 37°C for 5 hours following which the membrane was removed from the chamber, placed in ethanol for 15 seconds, and air dried. Membranes were stained with haematoxylin for 30 minutes, washed in cold water, and mounted on a glass slide. Migrated cells on the undersurface of the membrane were counted in 20 high power fields (×1000) per well. Each assay was carried out in triplicate and a mean value for migration obtained.

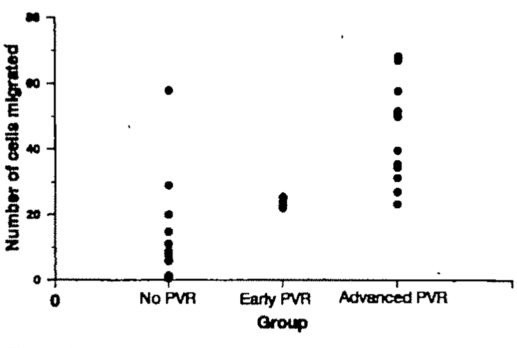

Figure 2 A scattergram showing the number of fibroblasts migrated to vitreous from the different groups of PVR.

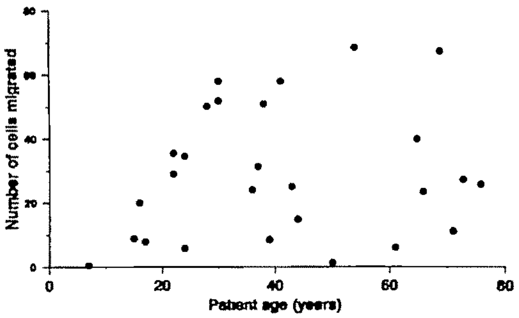

Figure 3 A scattergram showing the number of cells migrated against the patient age.

ELECTROPHORESIS

Samples of vitreous (1 μl) were analysed by SDS-PAGE electrophoresis. Samples were run under reducing and non-reducing conditions (with or without mercaptoethanol in the sample buffer). In addition native PAGE of vitreous samples was performed. Gels were stained with Coomassie blue dye.

FIBRONECTIN ASSAY

Levels of fibronectin in the vitreous in 13 samples were measured using an enzyme linked immunosorbent assay (ELISA). Ninety six well microtitre plates were coated overnight with 100 μl of rabbit anti-fibronectin antibody (Dakopatts, UK) diluted 1:1000 in phosphate buffered saline (PBS). The plates were then washed three times with PBS/Tween and coated with 200 μl of 3% bovine albumin in PBS at 37°C for 1 hour to prevent non-specific binding. The plates were then washed with PBS/Tween and 20 μl of vitreous sample were placed in three wells and made up to 100 μl with PBS/Tween. The vitreous samples were diluted 1 in 5 so that the evaluations fell within range of the exponential part of the standard curve. Standards were made up from human fibronectin (Sigma, Poole, UK), and run in the same experiment.

The samples were incubated at room temperature for 2 hours after which the plates were washed with PBS/Tween and 100 μl of rabbit antifibronectin conjugated to peroxidase (Dakopatts, UK) 1:500 with PBS/Tween was added to each well and incubated for 1 hour at room temperature. The wells were washed with PBS/Tween and a colour reagent (tetra-methyl benzidine HCl) citric acid and 5 μl of H_2O_2 were added. The colour reaction was stopped with

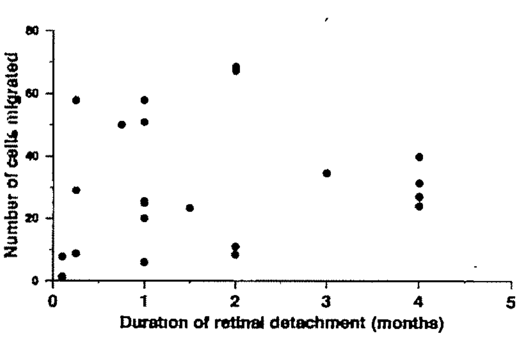

Figure 4 A scattergram showing the duration of retinal detachment against the number of cells migrated.

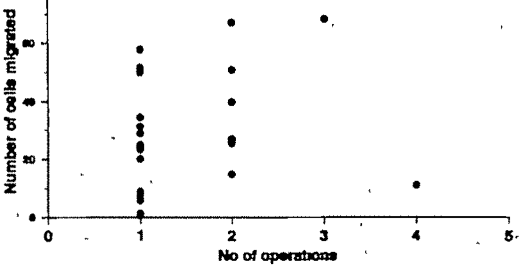

Figure 5 A scattergram showing the number of cells migrated to each vitreous against the number of retinal detachment operations.

molar H_2SO_4 and the absorbance measured on an automated ELISA reader.

STATISTICS

All data from the migration assays were expressed as the mean with the standard error of the mean. The statistical significance of the vitreous-related changes was examined by *t* tests and one way analysis of variance (Minitab Software, Minitab Corp, USA).

Results

MIGRATION ASSAY

There was a wide variability in the fibroblast migration to vitreous aspirates with as much as a ten-fold difference in results. However the vitreous aspirates from group 3 patients (advanced PVR) stimulated fibroblast migration to a much greater degree than vitreous aspirates from group 1 (no PVR) although wide scatter in migration results was observed in the latter group. Vitreous aspirates from group 3 stimulated a mean of 44·7 (SD 15) fibroblasts to migrate whereas group 1 stimulated 14·3 (SD 15) fibroblasts to migrate. This difference was statistically significant $p<0{\cdot}0001$ (Fig 2).

There appeared to be less migration induced by the vitreous aspirates in group 2 (early PVR) compared with group 3 (advanced PVR) but the numbers of samples in the former group were too small for statistical analysis.

We also correlated fibroblast migration against the age of the patients, the duration of retinal detachment, and the number of previous retinal detachment surgical procedures. In all three cases there appeared to be no close relationship (Figs 3, 4, 5).

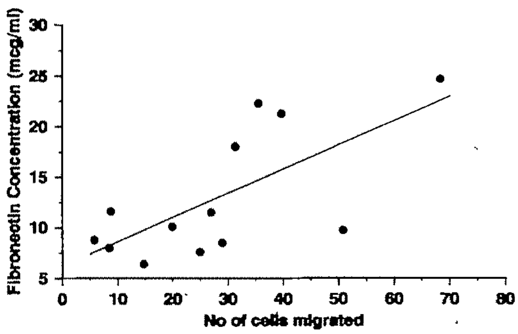

Figure 6 A scattergram showing the number of migrated cells against the fibronectin levels in the vitreous samples.

GEL ELECTROPHORESIS

Analysis of vitreous samples by gel electrophoresis from eyes with no PVR showed a smaller number of peptide bands compared with eyes with advanced PVR, and the cellular migration to vitreous samples was proportional to the number of peptide bands. However no particular band distinguished the vitreous samples which stimulated more cellular migration.

FIBRONECTIN ASSAY

There was a positive correlation between the measured fibronectin levels in vitreous aspirates and the migration of fibroblasts to the vitreous ($r=0{\cdot}68$, $p<0{\cdot}004$) (Fig 6) with a mean of 12·96 μg/ml and standard deviation of 6·29 μg/ml (range 6·4 μg/ml to 24·75 μg/ml).

Discussion

This study demonstrated that vitreous aspirates from eyes with advanced PVR stimulate fibroblast migration to a greater extent than vitreous aspirates from eyes with no PVR. This is due to the presence of chemoattractants in the aspirates from the eyes with PVR. From the evidence that fibroblasts may play a role in PVR[9, 10] the study of fibroblast migration in vitro may have clinical relevance with respect to PVR.

Clinically the development of PVR is encouraged by the presence of large areas of exposed retinal pigment epithelium, intraocular blood, or inflammatory exudate,[17, 19] conditions which were actually present in 11 of the 12 patients in group 1 (that is large or giant retinal tears and intraocular foreign bodies). The wide scatter of results in group 1 may be related to the diverse nature of the retinal detachments occurring in this group. However the fact that the chemoattractant properties of the vitreous aspirates from the 'non-PVR' eyes were generally lower than the established PVR eyes suggests that fibroblast migration may play a role later in the pathogenesis of PVR than other cell types (for example RPE cells, macrophages) and that fibroblasts could be recruited by the presence of such cells; this is an area of future research. This relatively late recruitment of fibroblasts akin to the situation in wound healing may also explain the apparent lack of a relationship between migration and both duration of retinal detachment and the number of surgical procedures. Furthermore although the number of patients was small the relatively low level of migratory activity observed in group 2 (early PVR) might also be explained by this hypothesis.

More difficult to explain however is the absence of a relationship between patient age and the migration of fibroblasts, since there is experimental evidence from work on other tissues that healing processes occur more vigorously in youth.[20, 21] This may be related to the complex nature of epiretinal membrane formation compared with scar development elsewhere.

Previous studies have shown increased concentrations of fibronectin in vitreous aspirates of eyes with PVR compared with those with retinal detachments without PVR.[4, 5, 9, 11–14] Fibronectin is produced by fibroblasts and one would predict that it would be present in highest concentrations in the vitreous of eyes with advanced PVR where fibroblasts (or RPE cells with fibroblast-like characteristics) are present. Of interest are the two high results for migration to vitreous observed in group 1 which occurred in the two eyes which had sustained penetrating injuries with intraocular foreign bodies. One can speculate that fibroblasts may well have entered the vitreous at the site of perforation.

Fibronectin is also known to be chemotactic for fibroblasts as well as other cell groups, and our observation of a strong positive correlation with fibroblast migration would accord with this.[4,5,9,11–13] In addition there is the evidence of inhibition of experimental PVR by a synthetic peptide derived from the cell-binding domain of fibronectin.[22] This peptide appears to prevent the attachment of RPE cells to vitreous and internal limiting membrane.

However the absence of any single band on gel electrophoresis which could be related to increased migration suggests that no single chemotactic factor including fibronectin is responsible. Other putative chemotactic agents for fibroblasts include the peptide factors, platelet derived growth factor, and transforming growth factor beta[23–27] but there are likely to be others.

Fibroblast chemotaxis is probably a later event in the pathogenesis of PVR, a condition which when advanced can be difficult to treat. Further understanding of the early events in the pathogenesis of PVR before fibroblast migration has occurred may provide a means of therapeutic intervention.

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Multifocal amelanotic conjunctival melanoma and acquired melanosis sine pigmento

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Abstract

Clinical and histopathological features of four cases of multifocal amelanotic malignant melanoma of the conjunctiva in association with 'acquired melanosis sine pigmento' are reported. The absence of conjunctival pigmentation in this extremely rare combination of lesions prevented early diagnosis and clinical monitoring. As a result orbital exenteration was required in three cases. This multicentric non-pigmented variety of conjunctival malignant melanoma tends to present later than pigmented forms and may require exenteration of the orbit as a primary procedure.

Malignant melanoma of the conjunctiva is uncommon but is among the most serious of ocular malignancies. The diagnosis of conjunctival melanoma is a challenge to both the ophthalmologist and pathologist. In addition the management of this neoplasm remains in dispute.

Usually conjunctival melanomas present as pigmented lumps, which may arise spontaneously (de novo), in a pre-existent naevus, or in association with primary acquired melanosis (PAM) with atypia, a unilateral, precancerous melanocytic condition.[1] Sometimes a combination of precursors is encountered.[1] The degree of pigmentation of such tumours depends on the amount of melanin in the tumour cells, macrophages, or in the extracellular matrix.

There has been only one well-described case report of a recurrent multifocal pigmented malignant melanoma of the conjunctiva originating in amelanotic acquired melanosis of the conjunctiva.[2] Griffith *et al*[2] referred to the amelanotic precursor as 'acquired melanosis sine pigmento'. Jackobiec *et al*[3] encountered a further four cases of multifocal conjunctival melanoma in association with amelanotic PAM, but did not mention the degree of pigmentation of the malignant melanomas.

We studied the clinical and histopathological features of four cases of multifocal amelanotic conjunctival melanoma arising in association with acquired melanosis sine pigmento.

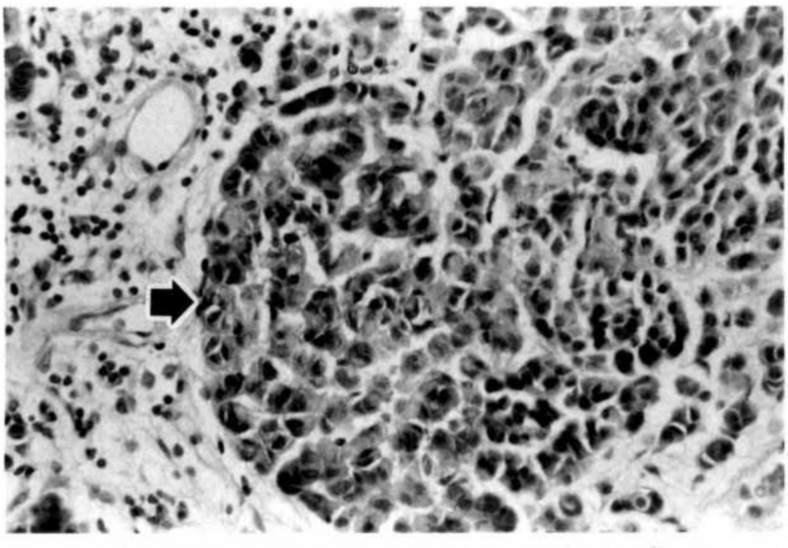

Figure 1 Case 1. Histology of exenteration specimen showing amelanotic malignant melanoma (arrow). Note the dark staining irregular nuclei and the complete absence of intracytoplasmic melanin pigment granules.

Case reports

CASE 1

A 39-year-old plastics worker presented with a multifocal amelanotic conjunctival melanoma of his left eye in 1986. Five years earlier hot oil had been squirted into this eye by accident. Despite immediate treatment he was left with a chronically irritable eye. Two years earlier an ophthalmologist had excised a small black spot in the left inner canthal region. The histological diagnosis was then reported as 'benign cellular naevus' but subsequent review of the sections showed malignant melanoma.

On examination there were multifocal pale pink fleshy lesions involving the entire limbal area and the upper and lower palpebral conjunctiva. One small patch of pigmentation at 12 o'clock was noted. Biopsies of multiple sites showed amelanotic malignant melanoma and primary acquired melanosis with atypia. A systemic metastatic evaluation was negative. The left orbit was then exenterated using a lid splitting technique. Histological examination showed multicentric amelanotic malignant melanoma (Fig 1) with a maximum thickness of 1 mm in the superior palpebral conjunctiva. The resection margins were clear.

In 1988 needle biopsy of a left preauricular mobile swelling, which had been growing for 6 months, showed melanotic malignant melanoma. The lump was subsequently removed by partial superficial parotidectomy. A course of local radiotherapy was given to the parotid and deep cervical nodes and when the patient was last seen in 1991 no signs of local or distant metastases were noted.

CASE 2

In 1986 a 45-year-old man, who also worked in a plastics firm, presented with a 6 month history of a gradually enlarging white mass on his right cornea. On examination there was a 4×5 mm elevated amelanotic tumour (Fig 2) with a smooth surface and large feeder vessels. A mild

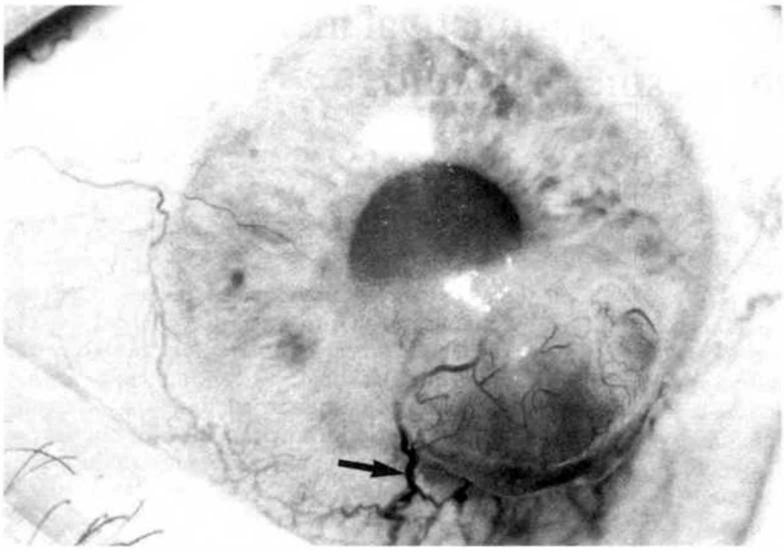

Figure 2 Case 2. An elevated amelanotic anaplastic malignant melanoma (4×5 mm) on the cornea of the right eye: a very unusual site for such neoplasm. Note the large feeder vessels (arrow).

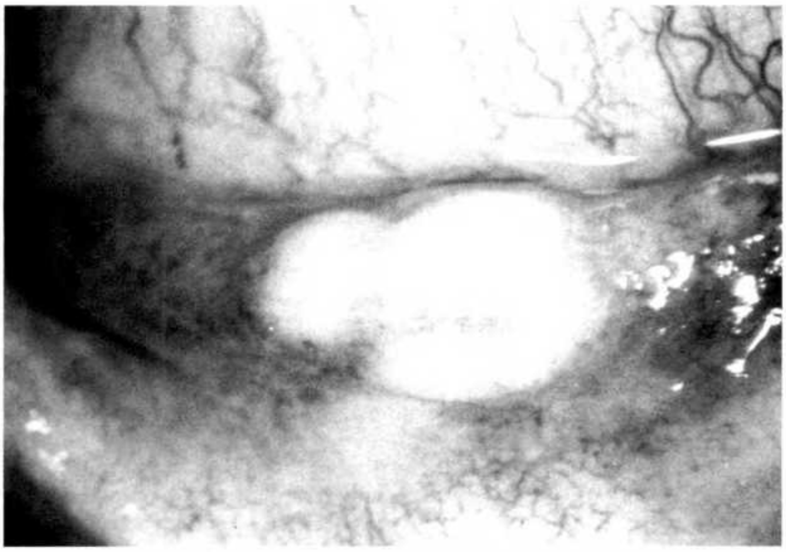

Figure 3 Case 2. A 2·5×5 mm white multinodular malignant melanoma in the palpebral conjunctiva of the right lower lid.

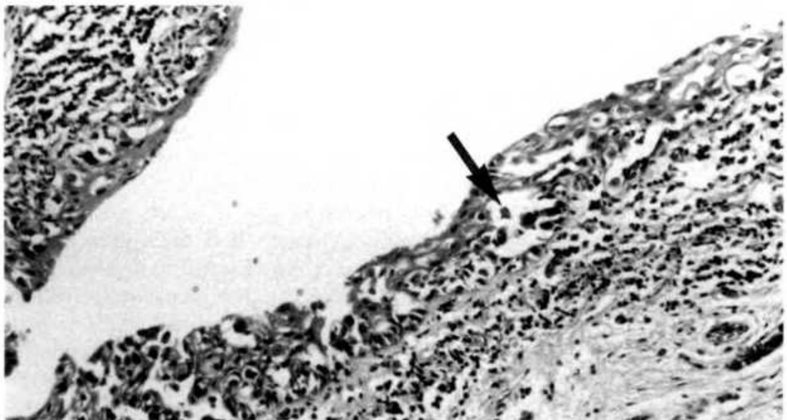

Figure 4 Case 2. Nests of amelanotic S-100 positive cells (arrow) in conjunctival epithelium.

degree of corneal epithelial infiltrate around the tumour was noted. The palpebral conjunctiva of both eyelids showed inflammatory signs and scarring. The left eye showed no abnormalities.

The corneal mass was resected using absolute alcohol to slide off the affected epithelium. Microscopic examination disclosed an amelanotic anaplastic malignant melanoma without evidence of any precursory lesion.

Seven months later superficial white deposits in the corneal epithelium and superior fornix were noted, and at follow-up no changes were observed until August 1988 when there was a 2·5×5 mm white multinodular tumour (Fig 3) in the palpebral conjunctiva of the right lower lid. Incisional biopsy showed an amelanotic malignant melanoma. There was no lymphadenopathy and a metastatic evaluation was negative. The right orbit was then exenterated and histological sections showed multifocal intraepithelial and subepithelial nests of amelanotic atypical S-100 positive tumour cells (Fig 4). When last seen in 1991 no signs of recurrent disease were noted.

CASE 3

A 54-year-old labourer presented with a 3 year history of intermittent redness of his left eye in June 1990. On examination there were multiple fleshy pink deposits involving the bulbar conjunctiva, the fornices, and the palpebral conjunctiva of both lids (Fig 5), and signs of chronic conjunctivitis, including large follicles and increased vascularity. Diagnostic biopsies revealed multicentric inflamed amelanotic S-100 positive malignant melanoma and areas of amelanotic primary acquired melanosis with atypia. The latter precursory condition was even detected in a biopsy of clinically unaffected conjunctiva. A systemic metastatic evaluation was negative and left orbital exenteration was performed in November 1990. When last seen in March 1991 there was no evidence of recurrence.

CASE 4

In 1987 a 46-year-old woman presented with a history of a longstanding pinguecula-like inflamed lesion in the temporal part of the left conjunctiva. Unresponsiveness to topical steroid treatment led to an excision biopsy which showed amelanotic epithelioid malignant melanoma and PAM with atypia. In the following years five nodular recurrences on multifocal sites around the limbus were excised or treated by β radiotherapy applied by a strontium-90 plaque (three doses of 800 cGy). When last seen in November 1990 there were no signs of recurrent disease.

Discussion

The absence of pigmentation in amelanotic primary acquired melanosis means that such a precursor may only be detected by biopsy and histological examination.

Jakobiec *et al*[3] observed that three out of four patients with multinodular malignant melanoma of the conjunctiva with microscopically extensive PAM sine pigmento had metastases and suggested these patients might have a worsened prognosis due to altered intrinsic biological features of the disease or problems in disease mapping. We think it is likely that amelanotic

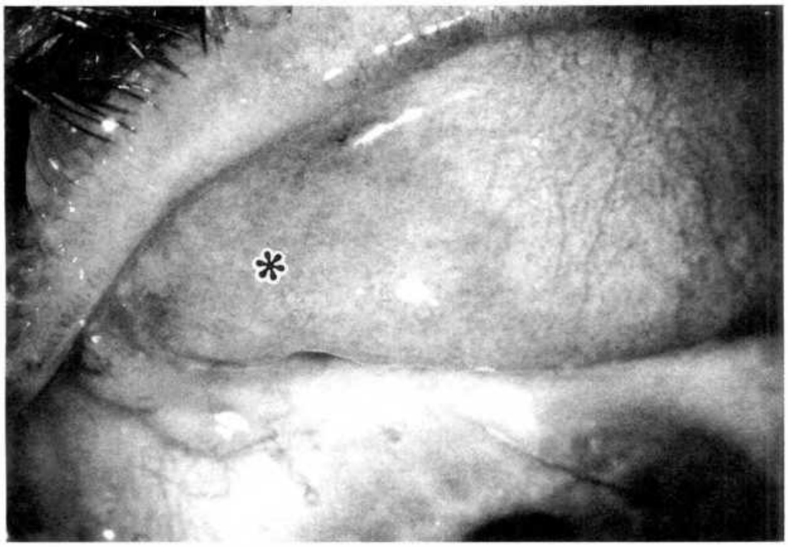

Figure 5 Case 3. One of multiple foci of fleshy amelanotic malignant melanoma (*) involving the chronically inflamed left upper palpebral conjunctiva.

tumours may defy early detection and reach a vertical growth phase, with the potential for metastasis. The risk of such spread is much greater if there is undetectable multifocal disease which may be undertreated by conservative management. Three of our patients with multifocal disease affecting unfavourable locations were radically treated by orbital exenteration and only one patient (case 1) had regional metastasis within 4 years of first presentation and 2 years of orbital exenteration. Although the period of follow-up has been limited, orbital exenteration in cases 2 and 3 may have prevented spread of conjunctival melanoma. The high rate of metastases in the patients reported by Jacobiec *et al*[3] who were treated with a combination of cryotherapy and surgery might have been related to initial conservative management.

Conjunctival melanoma originating from an area of PAM with atypia may develop at multiple sites, which makes its management more problematic. Folberg *et al*[1] found a median interval of 2·5 years between diagnosis of PAM with atypia and diagnosis of malignant melanoma. This interval enables the clinician to monitor such conditions, detect early progress to malignancy, and intervene promptly. However when the area of acquired melanosis is amelanotic the nature of this precursor may only become apparent when frank malignant melanoma has already developed, as is illustrated above. Multiple pink or white conjunctival nodules may give rise to diagnostic difficulties. Due to late detection and the difficulty of monitoring and assessing the extent of amelanotic melanoma and PAM sine pigmento some patients with this rare combination of lesions may require orbital exenteration as a primary procedure. However even this radical surgical treatment, which has been advocated by Reese[4] for all cases of biopsy proved invasive melanoma, may not prevent spreading of 'in-transit' metastases.

The absence of melanin in amelanotic melanoma and acquired melanosis sine pigmento is difficult to explain. It is of interest that in case 1 the first inner canthal lesion was pigmented, the subsequent multifocal nodules were amelanotic, and the preauricular metastasis was again pigmented. If the latter originated from the extensive amelanotic melanoma it would demonstrate the propensity of melanogenesis of at least one clone of the non-pigmented tumour cells. The production of melanin does not seem to be related to malignant potential, for melanomas with varying degrees of pigmentation have shown an ability to metastasise. The loss of the ability to make melanin may however signify a degree of dedifferentiation of tumour cells.

Jacobiec *et al*[3] found that several of their patients had a pre-existent naevus by history or in their pathological material. They speculated that naevus cells may have lost a certain potential of melanogenesis during malignant transformation and proliferation thus disguising the extent of the radial growth phase. In our series, however, there was a history of a potential naevus in only one case (case 4). In our opinion the multifocal nature of the disease described in our case reports does not fit with a theory of spreading transformed naevus cells.

It is unknown whether environmental factors play a role in the aetiology of conjunctival malignant melanoma and acquired melanosis. The patients in both cases 1 and 2 worked in the plastics industry. The patient in case 2 had been exposed to continuous plastics fumes at work and developed an amelanotic melanoma on the cornea, which is an unusual site for such neoplasm. The rarity of this tumour, the large number of chemicals to which patients were potentially exposed, and incomplete occupational histories make it very difficult to detect possible causative agents. Although the relation between occupation and conjunctival melanoma in cases 1 and 2 may well have been coincidental animal studies have demonstrated the propensity of certain chemicals to induce cutaneous malignant melanoma,[5,6] and similar induction and development of ocular malignant melanoma has been suggested.[7-10]

The purpose of this report has been to emphasise the capricious behaviour of conjunctival malignant melanoma. We have reported four cases of a previously undescribed combination of amelanotic melanoma arising in association with PAM sine pigmento. We believe that awareness of this non-pigmented variety of conjunctival melanoma is crucial for early recognition and management.

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MINI REVIEW

Bruch's membrane change with age

Age related macular disease is now the commonest cause of registered blindness in western communities,[1-4] and it is evident that the prevalence is rising with the increasing age of the population.[5,6] Both the realisation of the high prevalence of disease, and the prospects of therapy,[7-9] have stimulated recent interest in the disorder. Unfortunately it has now become evident that laser treatment will not have a major impact on blindness from age related macular disease.[10-12]

Since the historic monograph of Gass[13] there has been increasing clinical and laboratory research which has highlighted the role of neovascularisation and retinal pigment epithelial dysfunction in the pathogenesis of the disorder. However, there is still incomplete information on the natural history and the basic pathogenesis of age related macular disease, and the factors which determine the risk of visual loss are ill understood. There is now increasing circumstantial evidence that the chemical composition of deposits in Bruch's membrane may be an important determinant of the outcome of disease. It is hoped that current pathogenetic concepts will form a rational basis for future studies.

Nature of Bruch's membrane change

There is some evidence from microscopic studies that the chemical composition of Bruch's membrane deposits may differ from one subject to another. Conventional microscopy does not show large quantities of lipid in Bruch's membrane, since dehydration techniques tend to remove much of the lipid. Gaps in Bruch's membrane deposits have been thought to imply the presence of such lipid. Recently, by means of freeze drying techniques and histochemical staining, increasing quantities of lipid have been shown in Bruch's membrane with age. It was also demonstrated that the nature of the lipid differed from one patient to another.[14] Clinical studies imply that this may be relevant to disease.

The accumulation of debris in Bruch's membrane is a progressive phenomenon with age which may be detected by microscopy as early as 10 years, and is seen consistently by the age of 60 years.[15-18] This abnormal material is derived from the pigment epithelium,[18-22] and its accumulation is thought to result from failure to clear the debris discharged into this region.

The abnormal material may collect as discrete deposits in the inner portion of Bruch's membrane between the basement membrane of the retinal pigment epithelium (RPE) and the inner collagenous layer, which are recognised clinically as drusen. In addition diffuse accumulation occurs throughout Bruch's membrane. Thickening of the inner part of Bruch's membrane is compounded by excessive production of material resembling basement membrane by the pigment epithelium.[16,23]

Discrete Bruch's membrane deposits

Clinical studies have shown wide variation in the size and distribution of drusen from patient to patient, although there is remarkable symmetry between the two eyes of a single patient.[4,24,25] For example, in some patients the drusen may be confined to the central 5° in each eye, while in others the drusen occur in a circle 12–16° from the fovea, the fovea itself being free of visible deposits.

Drusen may be brightly fluorescent during angiography in some patients, while in others this is not the case; this characteristic is also symmetrical between two eyes.[25] There is doubt as to the determinants of fluorescence, and therefore the significance of this finding to disease. Fluorescence may be dependent on the quantity of pigment in the overlying pigment epithelium, or more importantly on the presence or absence of fluorescein within the drusen material. It has been hypothesised that hyperfluorescent drusen must have a high water content, allowing free diffusion of water soluble sodium fluorescein into the abnormal deposit; there may also be binding of sodium fluorescein to polar molecules.[26] By contrast the hypofluorescence of other drusen would imply that they are hydrophobic. It has been suggested that the former are rich in protein and phospholipids, while the latter are rich in neutral fats.

Diffuse Bruch's membrane deposits

To date there are no established clinical correlates of diffuse changes. A clue as to a possible sign of such deposits was derived from Sorsby's fundus dystrophy in which thickening of the inner portion of Bruch's membrane occurs.[27] A slow filling phase on fluorescein angiography is often the first sign of the abnormal phenotype,[28-30] though the nature of the association is unclear. There are two alternative sequences of events: either the vascular changes initiate the disorder, or the deposits influence the choroidal vasculature. Change of the choriocapillaris causing reduced clearance of waste material from the extravascular space, predictably would cause accumulation in the outer portion of Bruch's membrane. However, at least in Sorsby's fundus dystrophy this cannot be the case since the deposits are internal to the inner collagenous layer.[27] The alternative explanation is based on evidence that implies that the retinal pigment epithelium regulates the choroidal capillaries,[31,32] and the mechanisms by which this regulation may take place have been identified.[33] If the two cell systems are separated by a diffusion barrier, changes in the choriocapillaris might be expected as a consequence. Although few systematic analyses of the human choroidal vasculature exist, histopathological studies imply that reduction in its cross-sectional area is common in the elderly.[18,34,35]

This led to the concept that a prolonged filling phase of the choroid during fluorescein angiography may indicate the presence of diffuse Bruch's membrane thickening. Recently this angiographic sign has been demonstrated in a proportion of patients (26%) with age related Bruch's membrane change.[36] Thus, there is evidence that a slow filling phase may signal the presence of diffuse thickening of Bruch's membrane acting as a diffusion barrier between the retinal pigment epithelium and choroid in age related change.

Consequences of Bruch's membrane change

Clinical studies have been directed towards the analysis of discrete deposits on the inner surface of Bruch's membrane, and have largely ignored the potential importance of diffuse

Bruch's membrane thickening. Logically, the diffuse deposits would be expected to play a major role in determining the outcome of disease. However, it is fortunate that the chemical composition of two forms of deposit appear to be similar,[14] such that studies based on drusen characteristics may indicate also the influence of diffuse change.

The mechanisms by which the deposits cause the sight threatening complications have not been clearly identified. The major lesions causing visual loss are the growth of new blood vessels from the choroid through Bruch's membrane towards the retina, detachment of the retinal pigment epithelium, and atrophy of the outer retina and choriocapillaris.[10,37] Some correlation exists between the type of drusen and the form of lesion causing visual loss.

Drusen which are hyperfluorescent, and therefore presumed to be hydrophilic, appear to predispose to subretinal neovascularisation.[38,39] Over the last decade some determinants of blood vessel growth have been identified, though the circumstances leading to neovascularisation have not been defined. The chemical nature of the interfibre matrix of Bruch's membrane, change in the pigment epithelial influence upon blood vessel growth, and the presence of macrophages[40] which stimulate neovascularisation may all be relevant. In particular, polar molecules may stimulate invasion of Bruch's membrane by macrophages or neutral fats may suppress blood vessel growth.

Patients with large confluent drusen in the central area which are hypofluorescent have a predisposition towards pigment epithelial detachments rather than neovascularisation.[38,39] It has been proposed that these presumed lipid rich deposits reduce hydraulic conductivity of Bruch's membrane,[26,38,39] so that water which is pumped from the retina towards the choroid by the retinal pigment epithelium accumulates in the sub-pigment epithelial space. In its extreme form the pigment epithelial detachment becomes progressively larger, generating sufficient tangential stress in the detached tissues to cause a tear.[26,38]

Loss of photoreceptors in the outer neuroretina is a constant association with age.[22,41] Areas of well defined geographic atrophy supervene, a process which has been well documented histologically.[35] Atrophy may follow spontaneous resolution of retinal pigment detachments,[41] though this probably accounts for a small proportion of such lesions. To what extent a diffusion barrier is responsible for geographic atrophy is unknown. It is easy to conceive that movement of molecules between the choroidal capillaries and the pigment epithelium would be impeded by the interposition of a layer of debris particularly if it was composed largely of neutral fats rather than polar molecules. Just as the diffusion across Bruch's membrane of water and growth factors produced by the retinal pigment epithelium would be hampered, complexes containing molecules essential for photoreceptor function would not pass freely from the choroid to the retinal pigment epithelium. Consequent functional deficit might be expected. A search for sensitivity loss has been relatively unrewarding over discrete deposits,[42,43] but major and consistent deficit has been identified in those with the angiographic sign of slow choroidal perfusion, and therefore presumed diffuse disease.[44] There is good evidence that the circulatory disturbance alone would not cause ischaemic dysfunction.[17,45] The relevance to age related macular disease of the proposed barrier to diffusion at the level of Bruch's membrane could be tested by longitudinal study of patients who manifest the sign of a slow choroidal filling phase on angiography.

The symmetry of drusen in terms of quantity, distribution, and chemical composition, and the concept that the form of Bruch's membrane deposits determine the nature and magnitude of risk to vision, together suggest that the two eyes of a patient should behave in a similar manner, and that there would be differential risk from one patient to another. Several observations are compatible with this concept. In patients with unilateral visual loss there is the good correlation between the form of drusen in one eye and the type of lesion in the other.[38,39] It has also been shown in patients with a retinal pigment epithelial tear in one eye that there is a very high risk of a similar event occurring in the other.[46] With one exception,[47] all studies are compatible with an overall incidence of 10–15% per year of second eye involvement in patients with unilateral visual loss,[14,48-50] but, if the first eye had a tear of the pigment epithelium, the annual risk is much higher.[51]

Conclusions

From these data it appears that age related macular disease represents a continuous or discontinuous spectrum of disease in which patients behave differently one from another. There is circumstantial evidence that the chemical composition as well as the quantity of accumulated material in Bruch's membrane may determine the magnitude and nature of the risk to vision. Many clinically accessible clues exist which allow the variants of disease to be identified. Longitudinal studies are required to define better the natural history of the disorder, and these should take into account the proposed determinants of risk. The information derived from such research is essential to advance the pathogenetic concepts concerning age related macular disease further and to identify new therapeutic strategies. It is particularly encouraging that many of the recent concepts can be tested in the laboratory.

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CASE REPORTS

Perfluorocarbon heavy liquids in the management of posterior dislocation of the lens nucleus during phakoemulsification

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Abstract

We report a case in which the lens nucleus dislocated into the vitreous cavity through a posterior capsular rupture during phakoemulsification. We performed a vitrectomy and removed the lens nucleus using the perfluorocarbon heavy liquid perfluoro-1,3-dimethylcyclohexane. The management of posterior dislocation of the lens nucleus during cataract surgery is discussed.

One of the most serious peroperative complications of phakoemulsification is loss of the lens nucleus, either intact or in fragments, into the vitreous cavity. If it is left there, persistent intraocular inflammation and secondary glaucoma may ensue,[1] so it is desirable to remove the lens nucleus either at the time of the cataract surgery or as a secondary procedure. Hitherto three options have been available to the surgeon in this situation:

(1) Upward displacement of the lens nucleus with a viscoelastic agent. This carries the risk of vitreoretinal traction, retinal break formation, and subsequent retinal detachment and can be considered only if the nucleus is in the anterior vitreous.

(2) Vitrectomy followed by Fragmatome removal of the lens nucleus. Some nuclei may be too hard for this, and there is a risk of iatrogenic retinal damage.

(3) Vitrectomy, fluid/air exchange and removal of the lens nucleus with a long reach endocryoprobe. This too can traumatise the retina, and in addition it causes severe corneal distortion and possibly endothelial cell damage.

Perfluoro-1,3-dimethylcyclohexane (Flutec PP3, ISC Chemicals Ltd, Bristol) is a clear, colourless, non-toxic perfluorocarbon liquid[2] which, with a density of 1·83 g/cm^3, is denser than water and the lens nucleus, both of which therefore float on it. In the case described we used it to procure the straightforward and atraumatic removal of a dislocated lens nucleus from the vitreous cavity.

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Case report

A 69-year-old woman underwent cataract extraction under general anaesthesia. She had no other ocular pathology. A scleral pocket incision was performed followed by a continuous tear capsulorrhexis. The lens cortex was hydrodissected from the capsule and phakoemulsification begun, but early in this part of the procedure the posterior capsule dehisced, and the surgeon was unable to prevent the lens nucleus from dislocating into the vitreous cavity.

The scleral section was closed with temporary sutures, and a total vitrectomy was performed along with removal of the remaining lens cortex and capsule, by means of a standard three-port pars plana technique. The lens nucleus, then lying on the posterior retina, was freed from the residual vitreous gel with the ocutome and Flutec PP3 perfluorocarbon heavy liquid was injected via a 20 gauge cannula through one of the sclerostomies into the vitreous cavity. This elevated the lens nucleus into the anterior chamber. The wound was reopened and the lens nucleus removed easily with a vectis. Approximately 6 ml of heavy liquid was used in total. After closure of the incision Ringer's solution was passed through the infusion canula into the eye and the heavy liquid removed via a flute needle. After a pause to allow any perfluorocarbon retained in the residual vitreous gel to sink posteriorly, the exchange was completed and the sclerostomies closed. Postoperatively there was no excessive uveitis or rise in intraocular pressure, and after 4 months' follow-up the corrected visual acuity is 6/12.

Discussion

Loss of the lens nucleus through a ruptured posterior capsule is a risk not only during phakoemulsification but also in conventional extracapsular surgery. It is a rare complication, but the consequences for vision can be devastating if phakoanaphylactic glaucoma supervenes. The incidence of glaucoma seems to increase dramatically if the lens nucleus is allowed to remain for longer than 3 weeks,[3] so it is our belief that the nucleus should be removed surgically within this period.

If, following posterior capsular rupture, the lens nucleus remains anterior to the capsule, it is usually possible, after clearing vitreous from the anterior chamber, to manipulate it bimanually in the iris plane (with a cyclodialysis spatula passed through an anterior chamber paracentesis) and remove it with the phakoprobe or fragmatome. A nucleus in the anterior vitreous can be elevated into the iris plane with a viscoelastic agent and then removed in the same way. However, a nucleus lying on or near the retina will require a different approach. The timing of this surgery depends on the state of the vitreous gel. In patients over the age of 65 years it is likely that the posterior hyaloid is detached (and the risks of vitrectomy therefore much diminished), in which case the nucleus can be removed as a primary procedure as we have described here. In younger patients anterior vitrectomy should be performed to clear vitreous from the anterior chamber, and the section closed. The lens nucleus should then be removed as a secondary procedure, preferably within 3 weeks, by which time the posterior vitreous should have detached spontaneously.

Perfluorocarbon liquids were introduced into ophthalmology in the 1980s and are used in the management of complicated retinal detachments and for epiretinal membrane dissections.[4,5] They are clear, colourless, and have refractive indices similar to that of normal saline. They have low viscosity and therefore pass easily through small cannulae, while their high interfacial tension hinders their passage through retinal breaks.[4] Perfluorocarbon liquids are non-toxic when used short-term as a surgical tool, but should not be left in the eye, as long-term toxicity has been demonstrated.[6-8] The use of perfluorocarbon liquids in this situation relies on their being denser than the lens nucleus; thus the nucleus is displaced anteriorly, rendering it more easily accessible for removal. We have also used perfluorocarbon liquids in the management of traumatic dislocation of the crystalline lens, and the technique could be used to remove a displaced intraocular lens implant, as Flutec PP3 is denser than polymethylmethacrylate (Bacon AS, Lavin JM, personal communication). It is important to stress that they cannot be used without first performing a vitrectomy.

If small fragments of lens nucleus are displaced posteriorly, then a conservative approach may be adopted. A whole nucleus or larger fragment should be removed by vitrectomy and perfluorocarbon heavy liquid used either as a primary procedure if the patient is over 65 years old, or as a secondary procedure if the patient is younger or vitrectomy facilities are not immediately available.

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Senior-Loken syndrome. Case reports of two siblings and association with sensorineural deafness

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Abstract

Two siblings with Senior-Loken syndrome are described. The need for a full evaluation of renal function and hearing in children with a retinal dystrophy is emphasised.

Early onset rod cone dystrophies have been described in association with a number of renal lesions. The most common is that associated with nephronophthisis (medullary cystic disease). We report two siblings with the triad of nephronophthisis, retinal dystrophy, and sensorineural hearing loss.

Case reports

Two siblings (the older female, the younger male) were the products of a first cousin marriage between parents of Indian subcontinent origin.

CASE 1

The girl presented at 2 years of age with nystagmus. Vision was reduced in both eyes and the nystagmus was rapid, fine, horizontal, and pendular. There was a low myopic refractive error and the fundus was within normal limits. A diagnosis of autosomal recessive achromatopsia was made.

By the age of 9 years she complained of poor vision particularly in dim light. Her visual acuity was counting fingers at 7 feet (2 m) in the right eye and at 10 feet (3 m) in the left eye. Near vision was N36 in each eye. Colour vision was normal. Rapid, fine, horizontal pendular nystagmus was still present. Examination of the fundi showed narrowing of the retinal arterioles and pink optic discs with no pigmentation.

An electroretinogram (ERG) was performed at this time which showed no response. The diagnosis was revised to Leber's congenital amaurosis.

Audiological testing at this time demonstrated mild to moderate sensorineural hearing loss.

The following year she presented with fatigue, pallor, and nocturia. There was glycosuria and generalised aminoaciduria characteristic of a renal tubular defect. Her haemoglobin was 62 g/l and her creatinine clearance 2·5 ml/min/1·73 m.

Renal ultrasound showed slightly shrunken kidneys and numerous cysts in the corticomedullary region. A renal biopsy showed severe chronic tubulointerstitial nephritis and global glomerulosclerosis affecting more than 90% of the glomeruli. Immunofluorescence was negative for immunoglobulin and complement.

On electron microscopy there was thickening of tubular basement membrane which was split into multiple layers. The glomerular basement membrane was normal.

The diagnosis of end stage renal failure secondary to nephronophthisis was made and peritoneal dialysis was started. Ophthalmic examination at this time showed a visual acuity of perception of light only in the right eye and 20/200 in the left eye. The nystagmus was now coarse and slow but remained pendular. The anterior segments were normal with no evidence of keratoconus or lenticonus. The refractive error was −5·50 DS/+1·25 DC×090 in both eyes. The optic discs were now pale and arterioles were attenuated. There was no evidence of retinal pigmentation or white spots in the fundus.

Her sensorineural hearing loss had become more profound, and she was fitted with bilateral hearing aids.

CASE 2

The brother of case 1 was seen at the age of 6 months when his sister first presented. He did not fixate or follow unless the target was large. There was rapid fine horizontal pendular nystagmus. There was a low hyperopic refractive error and the fundus was within normal limits.

Over the next few years global developmental delay became apparent and a seizure disorder developed. A computed tomographic (CT) head scan was normal.

An abdominal ultrasound at age 7·5 years showed his kidneys to be of normal size and to contain corticomedullary cysts. Renal biopsy was similar to his sister's but showed less advanced disease. He was found to have moderate sensorineural hearing loss. At 7·5 years his ophthalmic examination showed him to be able to follow a light and to have positive optokinetic nystagmus (OKN) in each eye. Nystagmus was fine, horizontal, and jerky. The anterior segments were normal with no keratoconus or lenticonus, and the refractive error was −1·00 DS/+2·00 DC×090 in the right eye and +1·00 DS in the left eye. The fundi showed pale discs with attenuated vessels and no white spots or pigmentation.

Discussion

Senior in 1961[1] described a family where six of 13 children had nephronophthisis and tapetoretinal degeneration indistinguishable from Leber's amaurosis.

Loken in the same year[2] described two siblings of non-consaguineous parents. One had mental retardation and seizures and was blind with normal appearing fundi. The second sibling was also blind with normal appearing fundi but was of normal intelligence. Both siblings had severe renal failure and at biopsy their kidneys showed renal tubular atrophy and dilatation. Pathological examination of the eyes showed no identifiable photoreceptors and normal retinal pigment epithelium. Nephronophthisis is an autosomal recessive condition which presents with end stage renal failure in childhood.[3] Histological examination of the kidneys showed fibrosis or dilated tubules with thickened tubular basement membrane.[4] There are often secondary changes in the glomeruli and cysts are present at the corticomedullary junction.

Nephronophthisis may be associated with hepatic fibrosis[5] and may be familial. There are a number of ocular syndromes associated with nephronophthisis. Senior-Loken syndrome refers to nephronophthisis and retinal dystrophy. This combination in conjunction with skeletal dysplasia with cone shaped epiphyses is referred to as Saldino-Mainzer syndrome.[6] Nephronophthisis, retinal dystrophy, severe deafness, diabetes mellitus, and obesity constitute Alstrom syndrome.[7] Retinal dystrophy, skeletal deformities, and respiratory insufficiency are seen in Jeune's dystrophy.[8] In Bardet-Biedl syndrome nephronophthisis may be present.[9] Neither of the cases presented here had polydactyly or skeletal abnormalities other than mild renal osteodystrophy. Neither child was obese or diabetic.

The retinal lesion in Senior-Loken syndrome is variable and may be severe infantile onset retinal dystrophy[10 11] or a more typical retinitis pigmentosa.[12] Sector retinitis pigmentosa[13] and predominant cone receptor involvement have also been reported. In addition to the features of Senior-Loken syndrome the two cases presented here also showed moderate sensorineural hearing loss bilaterally. This has not been reported previously in association with nephronophthisis and retinal dystrophy and may represent a genetically linked condition.

These cases highlight the need for all children with a retinal dystrophy to have assessments of both their renal function and hearing.

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Orbital lymphoma in a patient with Felty's syndrome

Paul S Nassif, Steven E Feldon

Abstract

A 72-year-old woman presented with a diffuse infiltrating soft tissue mass involving the entire right orbit. She had a pre-existing phthisis of the right eye secondary to retinal detachment, and had developed painless proptosis on the same side. Her medical history included rheumatoid arthritis, leucopenia, and an enlarged spleen, characteristics consistent with the diagnosis of Felty's syndrome. Risk of lymphoma is thought to be higher in patients with established connective tissue disorders. The case described herein, to our knowledge, represents the first report of an association between Felty's syndrome and orbital lymphoma. The symptoms of Felty's syndrome in our patient were initially attributed to spread of a malignant process involving the orbit.

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Case report

A 72-year-old woman with pre-existing phthisis of the right eye secondary to retinal detachment developed painless proptosis on the same side. The proptosis was unresponsive to antibiotics or anti-inflammatory agents. Vision in the right eye was no light perception and a 4+ afferent pupillary defect was present. We obtained exophthalmometry readings of 29 mm on the right and 17 mm on the left, with a base of 110 mm. The left eye was normal. Magnetic resonance imaging (MRI) and computed tomography (CT) revealed a diffuse infiltrating soft tissue mass involving the entire right orbit. No bony changes were present and the sinuses were clear (Fig 1).

Systemic work-up demonstrated hepatosplenomegaly, a white blood cell count of $1{\cdot}8\times10^9$/l, haematocrit of 37·1%, and platelet count of 96×10^9/l with giant forms present. Serum antinuclear antibody (ANA) titre was positive at 1:80, rheumatoid factor was negative, and the angiotensin-converting enzyme level was normal. The sedimentation rate was 20 mm/h (Westergren). Tests for anti-DNA double strand antibody, anti-scleroderma antibody, and antibodies associated with Sjögren's syndrome were negative. We interpreted these findings as consistent with metastatic carcinoma or with disseminated lymphoma.

The physical examination prompted us to study further the patient's medical history. She then volunteered a history of rheumatoid arthritis, leucopenia, and an enlarged spleen. Medical records from 9 years prior to presentation showed strongly positive rheumatoid factor and a positive ANA titre. A white blood cell count of $1{\cdot}4\times10^9$/l, a platelet count of 181×10^9/l, and a broad-based polyclonal gammopathy were found. A bone marrow aspiration demonstrated myeloid and erythroid hyperplasia. Based upon these findings the patient had been diagnosed as having Felty's syndrome.

The orbital mass biopsy and subsequent work-up were diagnostic for a stage Ia large cleaved cell lymphoma of the B type, localised to the orbit (Fig 2). A 5 week course of 5000 cGy of local radiation therapy to the right orbit produced complete regression of the tumour by radioimaging studies.

Discussion

In 1924 Felty[1] reported five adults with chronic rheumatoid arthritis (RA) who had associated splenomegaly, leucopenia, and hypochromic anaemia, with or without a reduced platelet count. This syndrome occurs in less than 1% of patients with RA and is twice as common in women as in men.[2]

Patients with long-standing connective tissue

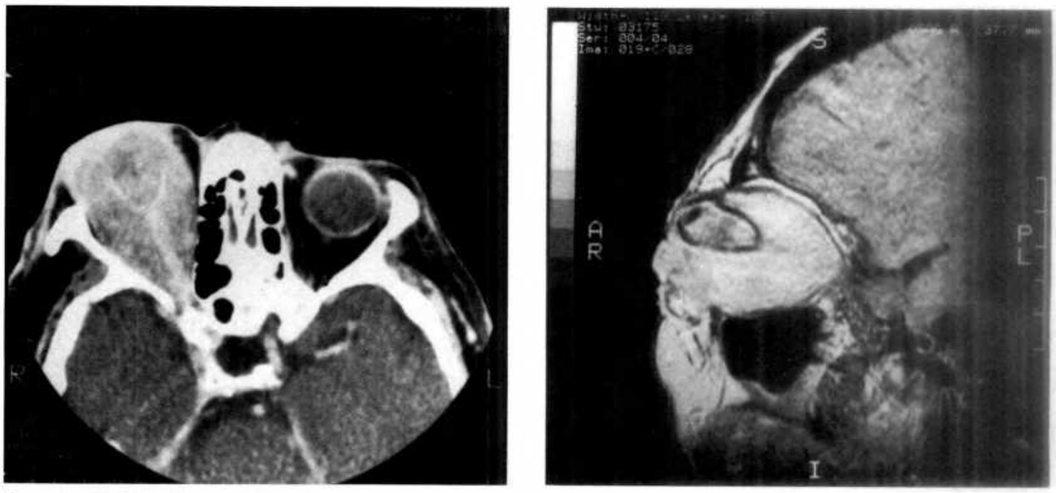

Figure 1 Diffuse infiltration of the right orbit, proptosis, and shrunken globe are demonstrated by axial CT scan (left) and by sagittal MRI (right).

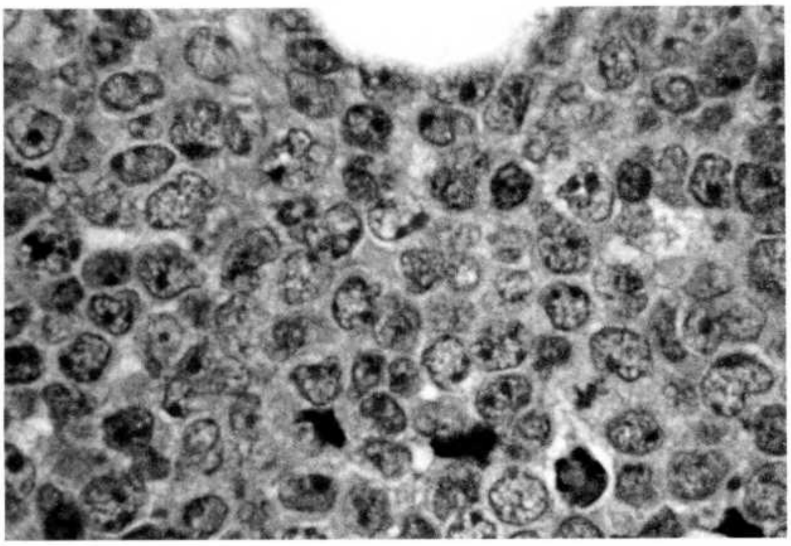

Figure 2 Photomicrograph of the orbital biopsy (×690) showing a large cleaved cell lymphoma of the B type. Clumping of nuclear material is prominent and occasional mitoses are seen. The white rounded spot at the top of the figure represents a fat globule.

disorders are thought to be at higher risk of developing lymphoma than is the general population.[3] For instance, patients with Sjögren's syndrome are about 44 times more likely to develop lymphoma than is the general population.[4] However the lymphomas associated with Sjögren's syndrome have been of the diffuse histiocytic type[5] rather than of the large cleaved cell variety found in our patient; furthermore antigen associated with Sjögren's syndrome was absent in our patient.

The development of lymphoma in the setting of long-standing connective tissue disease may be explained either by chronic immunostimulation leading to lymphoid hyperplasia and, eventually, to malignancy,[6] or by a disturbance in immune surveillance.

As orbital lymphoma associated with Felty's syndrome has not been previously reported, ophthalmologists should be alert to this diagnosis when evaluating patients with suggestive findings. In particular, the hepatosplenomegaly, neutropenia, and thrombocytopenia which often indicate diffuse spread of a malignancy may occasionally signify an underlying benign inflammatory process in association with localised lymphoma.

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Tuberculous keratoconjunctivitis

W A Aclimandos, M Kerr-Muir

Abstract

A 15-year-old West Indian boy had a left keratoconjunctivitis (KC) initially thought to be allergic in origin. He then developed a facial vesicular skin rash and a diagnosis of herpes simplex was suspected. Viral cultures were negative and there was a poor response to topical antiviral treatment. The KC progressed and became bilateral causing considerable reduction in the visual acuities. He complained of general fatigue and was pyrexial with generalised non-tender lymphadenopathy. There was a shadow in the upper lobe of the right lung. The bronchus was semioccluded by a non-caseating granuloma but no acid fast bacilli were found in the sputum or bronchial washings. In the presence of a strongly positive Heaf test, anti-tuberculous treatment was instituted which led to rapid resolution of all the systemic and ocular signs.

Case report

A 15-year-old West Indian boy with no significant history and apparently in good general health developed a sore, red left eye. He was born in the UK and had not been abroad. Treatment with topical antibiotics achieved only a slight relief of symptoms. On referral he was found to have limbal follicles with hyperaemia and moderate papillary reaction of the upper tarsal conjunctiva in the left eye. The visual acuities (VA) were 6/5 right and 6/6 left. He was diagnosed as limbal vernal and treated with sodium cromoglycate 2% drops.

Two weeks later he returned with a 3 day history of photophobia and swelling of both cheeks. The right VA was unchanged but the left was reduced to 6/9. There was a left central superficial corneal stromal infiltrate. He had raised, hyperaemic limbal lesions in both eyes. There was a vesicular rash around the nostrils with bilateral preauricular lymph node enlargement. Specimens from the conjunctiva and skin vesicles were obtained for serology and virus isolation. Treatment with topical acyclovir to the skin and the eyes was started.

One week later the left eye was painful and the VA reduced to 6/18. The skin rash had spread to involve the chin and the forehead. There was bilateral marked papillary conjunctivitis. The left cornea had a 1 mm diameter epithelial defect with an underlying infiltrate associated with an anterior uveitis. The preauricular, submental, and submandibular lymph nodes were enlarged. Mydriatics were added to the antiviral treatment.

Three days later the left eye became more comfortable. The epithelial defect had healed but the stromal infiltrate was deeper and denser. The left VA was 6/60. The right VA had also deteriorated to 6/18 and there were multiple corneal erosions with underlying stromal infiltration (Fig 1). There was a right endotheliitis and anterior uveitis. The patient was generally unwell with a temperature of 37·4°C and mild generalised lymphadenopathy. Virus isolation was negative. Serology did not show significant antibodies to *Chlamydia*, herpes virus, or adenovirus.

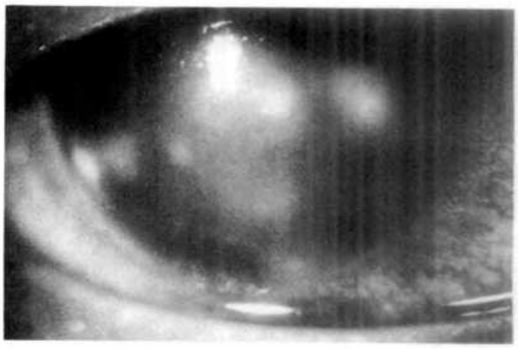

Figure 1 Tuberculous keratoconjunctivitis. Corneal erosions with underlying stromal infiltration.

Only mucoid and epithelial material with some polymorphs were found in corneal scrapes. Trypsin digest lid swabs grew *Staphylococcus aureus*.

Chest *x* ray revealed paratracheal and hilar lymphadenopathy with some consolidation in the anterior segment of the right upper lobe.

The IgE was 458 kilounits/l (normal, 20 kilounits/l), monospot (glandular fever test) was negative, ESR 37 mm/l per h and there was a 7% eosinophilia: 1·07 × 10^9/l (normal, 0·04–0·4).

The differential diagnosis of the skin lesions (Fig 2) included eczema or infected eczema while

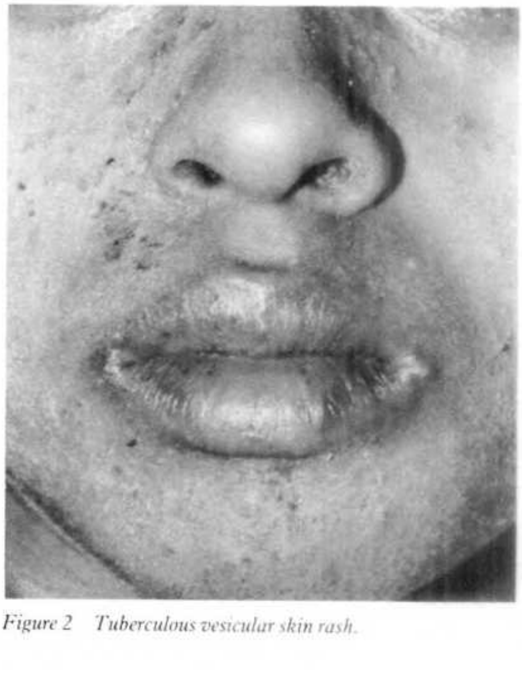

Figure 2 Tuberculous vesicular skin rash.

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the ocular manifestations could have been attributed to bilateral herpes simplex virus with atopy or keratitis secondary to staphylococcal hypersensitivity. However, considering the chest *x* ray findings it was felt that the underlying pathology could have been sarcoidosis or tuberculosis, the latter being more likely in view of the initial pyrexia. A presumptive diagnosis of tuberculous phlyctenular keratoconjunctivitis was made. This was supported subsequently by a grade IV positive Heaf test. The eye treatment was changed to topical prednisolone acetate 1%.

Repeated sputum samples were sterile. Bronchoscopy showed inflammation of the right upper lobe and bronchial dilatation with pus coming from the anterior segment. An unexpected finding was the presence of a papillomatous growth semioccluding the bronchus. Histology revealed a non-caseating granuloma. Stains for acid fast bacilli were negative.

Anti-tuberculous treatment was started with Rifater tablets (isoniazid, pyrazinamide, rifampicin). Over the following month the patient's general condition improved. The ocular inflammation and the keratitis resolved. The acuities recovered to 6/5 each eye.

Discussion

In England and Wales 7406 new cases of tuberculosis were notified in 1982.[1] The majority of cases occur in immigrants from the Indian subcontinent. The overall rate of tuberculosis for all ethnic groups is 18·3 per 100 000 population; the rate for the white ethnic group being 10·7; the Indian subcontinent group 38·2; and the West Indian group 31·2.[2] Other risk factors include drug addiction, diabetes, and old age.[3] AIDS could become an added risk factor.[4]

The morbidity and mortality from tuberculosis has declined steadily for several decades. This disease is now treatable and curable. However the diagnosis can be difficult particularly with extrapulmonary disease which is becoming more common[5] and can masquerade as various conditions.[3] Myocardial disease,[6] peritonitis,[7] meningitis,[8] chronic renal failure,[9] and pyrexia of unknown origin are some of the possible presentations. A wide range of conditions such as sarcoidosis, breast cancer,[10] and Crohn's disease[11] can also be mimicked by tuberculosis.

There are no specific tests apart from the recognition of the organism on histology or culture of a lesion, which is something rarely achieved with intraocular disease. Tissues are not easily obtainable and typical histology of granulomatous disease is rarely seen.[12] Current techniques require several weeks to months before cultures can be read.[13] Therefore in many cases the diagnosis is presumptive.

Ocular involvement in tuberculosis is comparatively rare[14] and the spectrum of presentation is very wide. There has been a relative decrease in the prevalence of tuberculous uveitis during the last 40 years.[15] There have been a number of ophthalmic cases reported because the diagnosis of tuberculosis was unsuspected. These range from a case of tuberculous uveitis presenting 34 years after a primary articular focus,[16] to cases where tuberculosis mimicked a retinoblastoma[17] or a pseudoglioma which, after enucleation, was diagnosed on histopathology to be retinal tuberculosis.[18] Phlyctens are probably the most common ocular manifestation of tuberculosis.[19]

It is important that while the rate of tuberculosis is falling our awareness of the disease and its widening spectrum does not. This relatively uncommon diagnosis is often difficult to confirm; however it should be particularly considered as a cause of phlyctenular keratoconjunctivitis.

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Microsporidial keratoconjunctivitis in a patient with AIDS

T W Metcalfe, R M L Doran, P L Rowlands, A Curry, C J N Lacey

Abstract

A male patient is described with acquired immune deficiency syndrome (AIDS) who developed chronic keratoconjunctivitis and chronic sinusitis due to infection with the microsporidian *Encephalitozoon cuniculi*. Diagnosis was confirmed by electron microscopic examination of conjunctival epithelial cells and nasal polypectomy specimens. Treatment with propamidine isethionate 0·1% (Brolene) eye drops six times daily led to a prompt resolution of the keratoconjunctivitis.

Microsporidia are small obligate, intracellular, spore forming protozoal parasites. The phylum *Microspora* consists of approximately 80 genera and more than 700 species.[1] They colonise a wide range of invertebrates and vertebrates including non-human primates though until the advent of acquired immune deficiency syndrome (AIDS) had only rarely been reported in man.[2-5]

Case history

A 22-year-old bisexual man was referred to the Genito-Urinary Department in 1986 having been found to be HIV antibody positive at routine screening following blood donation.

He first noticed mild ocular discomfort and blurring of vision in October 1988. His symptoms ran a chronic fluctuating course and failed to respond to several courses of topical antibiotics. He developed problems with nasal obstruction and discharge in February 1989.

He was referred to the Ophthalmology Department in June 1990. On initial examination best corrected visual acuity was 6/9 in each eye.

His conjunctiva was minimally injected with no follicular or papillary response. Both corneae were diffusely covered with fine punctate epithelial opacities the majority of which stained with fluorescein (Fig 1). There was also some punctate staining of the interpalpebral bulbar conjunctiva of both eyes. The anterior chambers and vitreous were quiet and fundal examination revealed an isolated cotton wool spot above the right macula.

Similarities between this case and recent reports from the USA of microsporidial keratoconjunctivitis in patients with AIDS were noted.[6 7]

Conjunctival scrapings were therefore taken from both eyes and sent for electron microscopic examination which established the diagnosis of *Encephalitozoon cuniculi* keratoconjunctivitis. Formal nasal polypectomy was performed at this time to relieve the patient's chronic nasal obstruction. Histological specimens showed *Encephalitozoon cuniculi* infection of the surface epithelial cells of the nasal mucosa.

Treatment of the keratoconjunctivitis with guttae propamidine isethionate 0·1% (Brolene) six times daily was begun on an empirical basis as this agent has been shown to be effective against other classes of protozoa.[8]

Relief of the patient's ocular symptoms and resolution of the punctate keratopathy with improvement of vision to 6/5 in each eye occurred within 3 weeks of commencing therapy with propamidine isethionate. Repeat electron microscopic examination of conjunctival scrapings was carried out which failed to reveal any infected cells.

After 2 months the patient stopped using propamidine isethionate eye drops and suffered a mild recurrence of his symptoms. Clinical examination revealed a recurrence of the punctate keratoconjunctivitis and further cytological studies showed reinfection of conjunctival epithelial cells with microsporidia.

Methods

Conjunctival scrapings from both eyes and nasal

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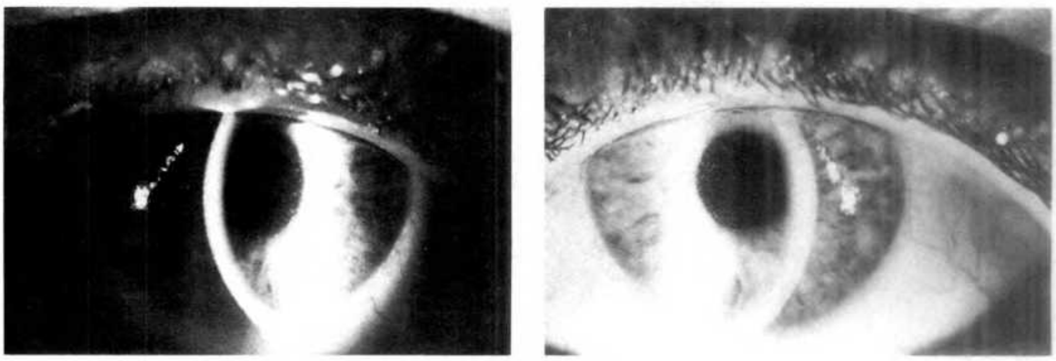

Fig 1A *Fig 1B*

Figure 1 Slit-lamp photograph of (A) left and (B) right corneae showing coarse punctate epithelial keratopathy.

polypectomy specimens were prepared in ultrathin sections and examined in an AEI EM801 electron microscope.

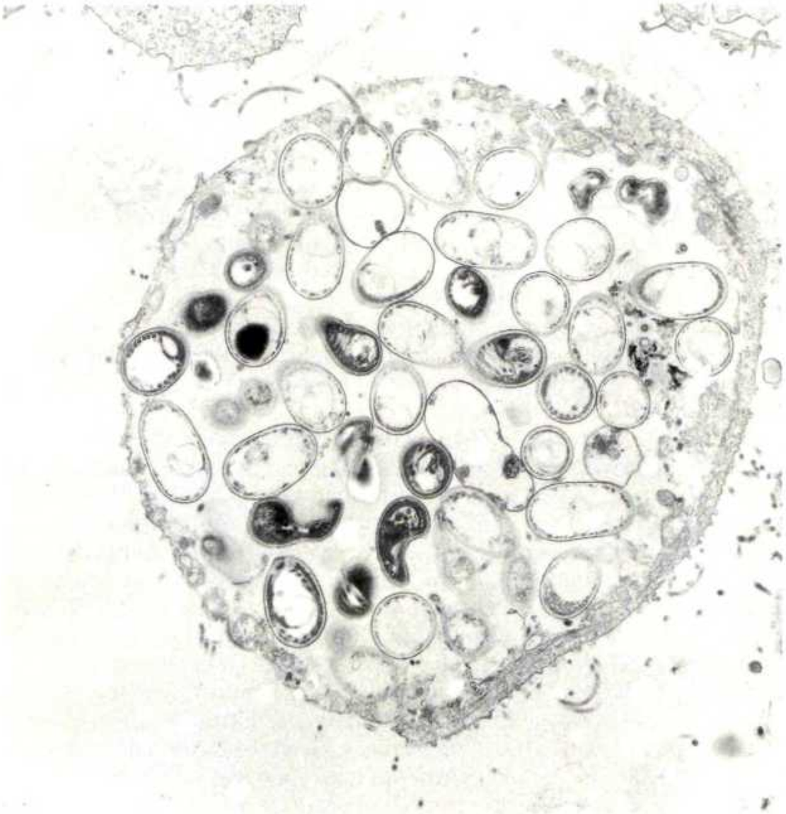

Figure 2 Electron micrograph of a conjunctival epithelial cell containing numerous Encephalitozoon cuniculi *spores within membrane-bound cytoplasmic vacuoles. (×5600.)*

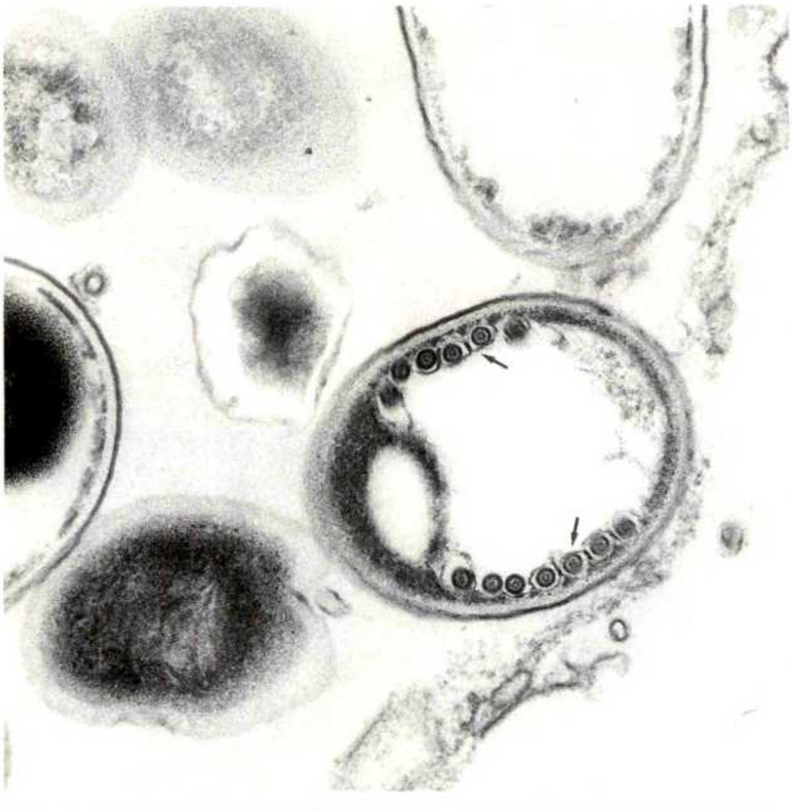

Figure 3 Electron micrograph of an Encephalitozoon cuniculi *spore showing characteristic coiled filaments (arrows). (×35 000.)*

Results

The conjunctival scrapings consisted of squamous epithelial cells; no inflammatory cells were seen. In the first sample the majority of epithelial cells examined from both eyes were infected with microsporidial spores contained within membrane-bound vacuoles (Fig 2). The spores were ovoid measuring 2 μm×1 μm. The spore wall was 60 nm thick and comprised an outer electron dense layer (exospore) and an inner electron lucent layer (endospore). A membrane lined the endospore which in mature spores enclosed an electron dense cytoplasm. Within the cytoplasm was a single nucleus and a peripheral coiled filament which emanated from a polaroplast organelle at the anterior pole of the spore. Six or seven turns were evident in the filament (Fig 3). Extruded filaments were seen in several spores. Less mature spores were more electron lucent with fewer internal organelles. Based on these ultrastructural findings the organism was identified as *Encephalitozoon cuniculi*.

Discussion

The characteristic feature of AIDS is recurrent opportunistic infections in the presence of an impaired cellular immune system. Classes of organisms previously rarely seen and of low pathogenicity have become common and behave in a virulent manner. We report a man with AIDS with keratoconjunctivitis and sinusitis due to infection with the microsporidial parasite *Encephalitozoon cuniculi*. This is the first case of microsporidial keratoconjunctivitis in a patient with AIDS described outside the USA. Microsporidial infection of the mucosae of the nose and nasal sinuses has not previously been reported.

We found a rapid clinical improvement in this patient's keratoconjunctivitis on commencing treatment with propamidine isethionate which was confirmed by cytological studies. We suggest that further study of this antimicrobial agent whose precise mode of action is unknown is required to assess its value in patients with microsporidial infections.

Although this form of treatment holds promise for relieving ocular symptoms in this infection the likely widespread involvement of other tissues especially respiratory mucosa provides a persistent reservoir for reinfection.

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British Journal of Ophthalmology, 1992, 76, 179–180

Exacerbation of akinetic seizures by atropine eye drops

Barry D Wright

Abstract

A case is reported where atropine sulphate eye drops increased the frequency of fits in a child suffering regular akinetic seizures. This increase was marked and observed during two separate courses of eye drops. This is discussed with reference to previous reports of central nervous toxicity after the use of topical atropine sulphate.

Case report

A 3-year-old otherwise normal blonde male infant suffered akinetic seizures. A typical seizure would involve him dropping to the ground with complete loss of tone without prodrome. He would then stand up almost immediately and carry on his activities. The attacks were infrequent happening only on a monthly basis unless the child had a fever in which case they occurred up to 10 times in 1 day. Two separate electroencephalograms at 6 month intervals (while not on medication) confirmed midline spike discharges of a nature sparsely reported in the literature.[4-7]

At the age of 18 months he attended a local eye clinic and required refraction for study of a squint. He received 1% atropine sulphate drops – one drop in each eye twice daily for 4 days. At this time he had up to 30 seizures per day for 5 days and these tailed off some 2 days after the course of drops had finished. The association with atropine at this time was thought to be coincidental.

At the age of 2 years and 6 months he once again received atropine sulphate 1% eye drops prior to refraction studies. Once again this was one drop in each eye twice daily for 4 days. Because of the previous association a much closer record was kept of events.

Twenty four hours after starting the eye drops he began to have an increase in seizures. Prior to the eye drops these had occurred on only two occasions in a 3 month period. After the eye drops had been started he was recorded as having 4, 22, 30, 25, 8, 2, and 1 fit on respective days. These were all akinetic seizures from which he recovered immediately. On subsequent days there was a return to the original pattern of seizures. There were no fevers or other illnesses at this time. It was noted that his pupils were dilated until the beginning of day 7 after starting the eye drops (that is 3 days after the drops were finished).

On a subsequent occasion when he required further refraction studies atropine was avoided. Cyclopentolate was used on a once only basis and resulted in no increase in seizures.

Discussion

After administration of eye drops absorption takes place through the conjunctiva and then after passage down the lacrimal system through the nasal mucosa, pharynx, and gastrointestinal tract. To limit this many centres use ointment rather than drops for children although there are still some centres (as in the clinic attended by this child) routinely using drops.

Serious side effects of topical atropine involving the central nervous system have been reported in the medical literature on many occasions.[1,2,8-23] Convulsions in association with topical atropine drops have only been reported to the Committee on Safety of Medicines through the yellow card system on one occasion since 1963,[24] but the literature suggests that they occur more frequently. As early as 1902 without reference to cases Rockcliffe[25] suggested that convulsions were 'not infrequently seen' with atropine eye drops and more recently Davidson has referred to the association 'particularly in children'.[3] Several case reports highlight the association usually in the context of wider central nervous toxicity.[1,8-11] None of these relate to exacerbation of existing epilepsy.

The frequent central spikes found on EEG in the child in this report mostly occurred without clinical correlation. Some animal studies have shown that the EEG can be affected by atropine. Large amplitude spikes may be produced[26] and the amplitude of existing spikes may be increased by up to 70%.[27] This would provide one model for an increase in the number of seizures suffered in this case. Atropine eye ointment would be expected to produce lower systemic concentrations of atropine than with eye drops and thus less likelihood of systemic reaction[3] and central nervous toxicity.

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Intermediate uveitis and Lyme borreliosis

Josefine Breeveld, Aniki Rothova, Herman Kuiper

Abstract

A case of chronic intermediate uveitis and associated classic snowbanking (pars planitis) with severe cystoid macular oedema probably due to Lyme borreliosis is reported. Despite a disease duration of 10 years the patient's ocular symptoms and visual acuity responded promptly to intravenous ceftriaxone treatment. This case demonstrates that periodic re-evaluation of patients with intermediate uveitis is necessary to obtain a specific diagnosis which may include Lyme borreliosis.

Ophthalmic manifestations of Lyme borreliosis can occur in every stage of the disease either in the presence or absence of other organ involvement.[1 2] The ocular involvement includes keratitis, uveitis, endophthalmitis, and various neuro-ophthalmologic symptoms. The cases of intermediate uveitis due to Lyme borreliosis reported so far have been associated with posterior synechiae and granulomatous anterior chamber inflammation.[1] We report on a patient with classic intermediate uveitis (pars planitis) and Lyme borreliosis.

Case report

In 1982 a 29-year-old man noticed a decline of visual acuity in both eyes. He consulted several ophthalmologists from 1982–84 but no ocular abnormalities were found which could explain his complaints. In 1984 he suffered from presumed bacterial keratitis in his left eye which was treated topically elsewhere.

In February 1985 he visited our department with complaints of conjunctival redness and blurred vision. History disclosed an amblyopic right eye due to esotropia. He had a refractive error of +6+1·5×120° RE and +6+1·5×170° LE. The corrected vision was 0·4 RE and 0·6 LE. Further ocular examination revealed a slight follicular conjunctivitis in both eyes, peripheral blue-dot lens opacities in both eyes with a clear visual axis, and no signs of intraocular inflammation. No abnormalities except conjunctivitis were encountered and no treatment was given.

In November 1985 he complained again of decreased vision. On examination a corrected vision was 0·4 RE and 0·5 LE was found and except for the blue-dot lens opacities there were no pathological findings.

In July 1987 he consulted us again with a progressive visual decrease. Visual acuity was 0·3 in both eyes. Further examination revealed flare and cells in the anterior chamber, blue-dot lens opacities, vitritis, peripheral snowbanking, and cystoid macular oedema (CMO) in both eyes (Fig 1). The fluorescein angiography confirmed the pars planitis and CMO and disclosed no signs of vasculitis or chorioretinitis. The results of the screening programme for uveitis (serum angiotensin converting enzyme, serum lysozyme, serological test for syphilis, Mantoux test, chest *x* ray) were all within normal range.

The diagnosis of idiopathic intermediate uveitis was made. Oral prednisone therapy was instituted because of the marked CMO. The visual acuity slowly improved to 0·4 both eyes and the inflammatory signs regressed within several weeks.

In December 1987 progressive visual loss occurred in LE due to massive retinal oedema with associated peripheral intra- and subretinal exudates. Cryocoagulation of the peripheral retina (snowbanks) LE was performed with favourable effect. In the following years the patient also received subconjunctival corticosteroid injections depending on his disease activity and his visual acuity varied between 0·3–0·5 RE and 0·3–0·6 LE.

In 1990 re-evaluation of the cause of uveitis revealed no abnormalities except for a positive antibody titre against *Borrelia burgdorferi* (indirect immunofluorescence assay 1:320). A detailed history concerning Lyme borreliosis was obtained. The patient recalled no tick bite. However in 1980 he noticed a droplet of blood on his left thigh. Several days later an expanding erythematous skin lesion occurred on this spot. Within 1 week severe radicular pain in both legs occurred. Because of this pain he could not walk nor sleep for 1 week. The pain abated in 1 month without any specific treatment.

Neurological examination in 1990 revealed no abnormalities. Analysis of cerebrospinal fluid showed normal leucocyte count, protein, and glucose concentration. No signs of intrathecal antibody production were found.

The history of the skin lesions was compatible with erythema migrans and the radicular pain

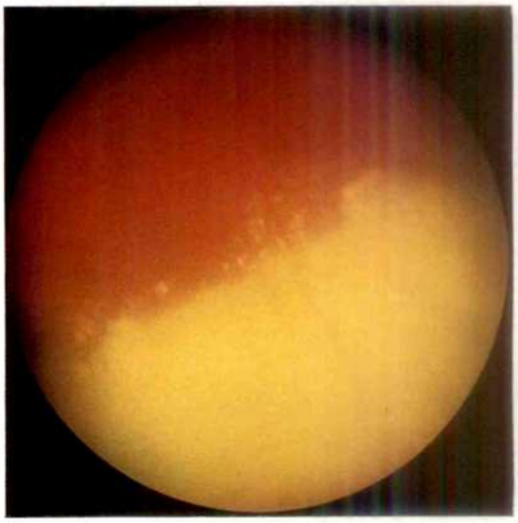

Figure 1 Intermediate uveitis with peripheral snowbanking in a patient with Lyme borreliosis (LE).

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might have been meningoradiculitis. A presumptive diagnosis of Lyme borreliosis was made according to CDC criteria.[3] Subsequently the patient was treated with ceftriaxone intravenously 4 g/day for 2 weeks with prompt response of ocular symptoms. In 2 months his visual acuity was improved to 0·5 RE and 0·8 LE and the active inflammatory signs vanished.

Discussion

Intermediate uveitis associated with Lyme disease has been described but in these patients the uveitis was complicated by posterior synechiae and granulomatous anterior chamber inflammation.[1] These anterior chamber symptoms are not regularly encountered in classic intermediate uveitis (pars planitis).[4]

Our case demonstrates that even a classic intermediate uveitis with a protracted course may be due to Lyme borreliosis. Our patient responded promptly to specific antibiotic therapy with ceftriaxone and despite the CMO over several years his visual acuity rapidly increased. We report this case to emphasise the following points: periodic re-evaluation of patients with intermediate uveitis is necessary to obtain a specific diagnosis which may include Lyme borreliosis. Furthermore chronic cases suffering from intermediate uveitis and long standing CMO due to Lyme borreliosis may benefit from adequate treatment.

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Orbital paraganglioma: case report and review of the literature

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Abstract

Paragangliomas of the orbit are extremely rare. A case of an orbital paraganglioma, including the first magnetic resonance imaging description of this tumour is described here. The patient underwent surgery with gross total removal of the tumour and relief of his initial chief complaint of visual blurring. The differential diagnosis and therapeutic options for the management of this tumour are discussed.

Paragangliomas are neoplastic growths of the non-chromaffin paraganglionic tissue which may arise in the abdomen, thorax, or head and neck region. Though paragangliomas of the head and neck are not uncommon they are rarely found in the orbit, where the site of origin is thought to be the ciliary nerve.[1] Indeed only 27 cases have been reported in the literature.[1-23] The present report gives details of such a case and provides the first compilation of all previously described orbital paragangliomas.

Case history

The patient is a 55-year-old man who presented to the Medical Center Hospital of Vermont with intermittent visual blurring during the preceding 6 months. Physical examination revealed slight hypertropia and exotropia of the right eye. Vision was 20/25 OS and 20/20 OD. Pupils were equal and reactive. Spontaneous venous pulsations were absent on the right and normal venous pulsations were present on the left.

The visual field on the right showed concentric constriction of isopters and a small superior defect at 40° out. Colour vision was noted as 10/14–12/14. A right afferent pupillary defect of about 1·2 log units was noted.

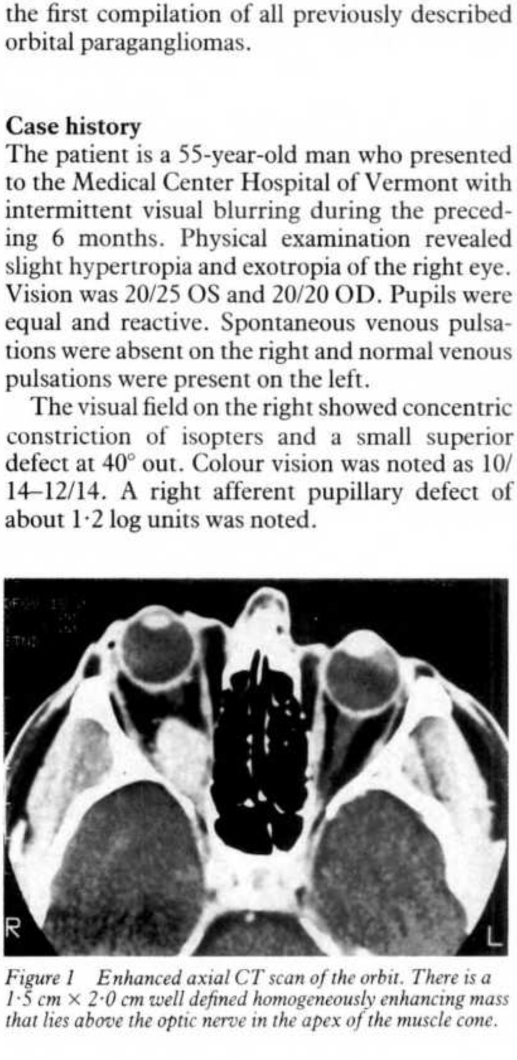

Figure 1 Enhanced axial CT scan of the orbit. There is a 1·5 cm × 2·0 cm well defined homogeneously enhancing mass that lies above the optic nerve in the apex of the muscle cone.

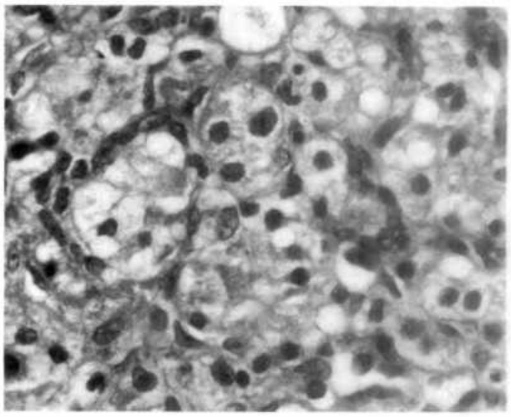

Figure 2 Nests of epithelioid cells in 'zellballen' pattern, characteristic of paraganglioma (haematoxylin and eosin, ×400).

Computed tomography (CT) of the orbits revealed a homogeneous mass lesion of 2 cm separate from and superolateral to the optic nerve. Prominent orbital veins were identified (Fig 1).

The patient underwent a right lateral orbitotomy with visualisation of a firm, well circumscribed mass with an adherent vascular capsule. Frozen section examination suggested the diagnosis of a meningioma. Therefore the operation was terminated after partial internal debulking of the mass with a plan for postoperative radiation therapy.[24]

Permanent microscopic sections of the tumour revealed nests of polygonal or spindle cells surrounded by a delicate fibrovascular stroma forming the so-called 'zellballen pattern' (Figs 2 and 3). The tumour cells were moderate in size and round to polygonal in shape. The nuclei were oval, slightly hyperchromatic, and pleomorphic. Mitoses were rare. Immunohistochemical staining revealed focal positivity of the

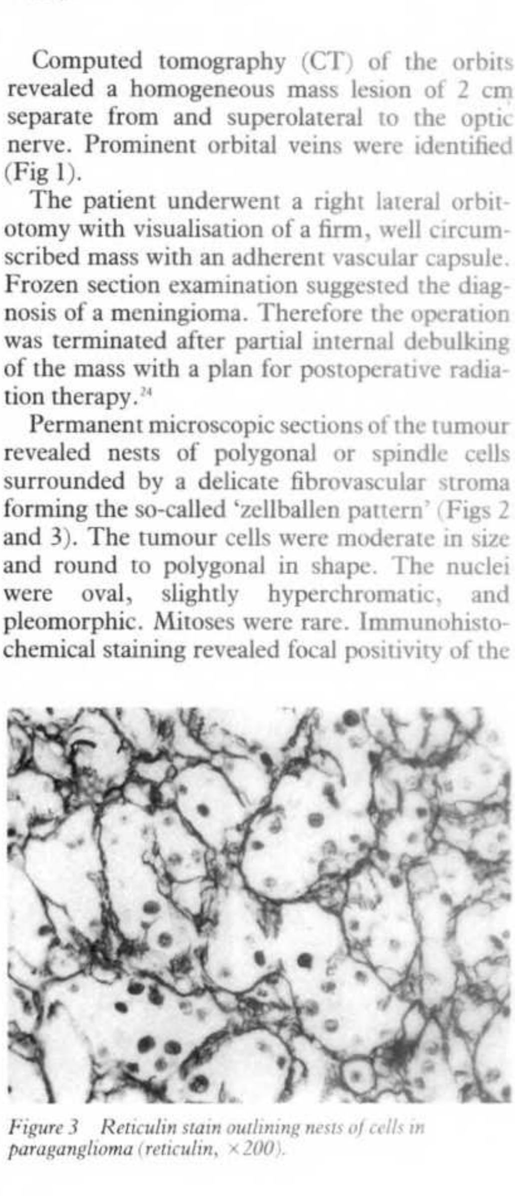

Figure 3 Reticulin stain outlining nests of cells in paraganglioma (reticulin, ×200).

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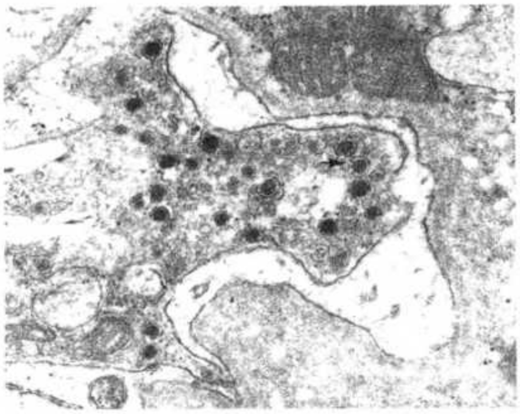

Figure 4 Dense core granules (arrow) within the cytoplasm of tumour cells (×11 500).

tumour cells for neuron specific enolase and chromogranin. Ultrastructural examination revealed occasional tumour cells containing scarce to many neurosecretory granules (Fig 4).

Six months postoperatively, a magnetic resonance (MR) scan (Fig 5) of the right orbit was obtained and demonstrated a 2·0 cm by 1·8 cm intraconal mass that displaced the optic nerve medially and inferiorly. The typical prominent vessels and 'salt-and-pepper' appearance of the MR image as described for paragangliomas of more typical locations were present.[25] Because of residual tumour and a recurrence of his diplopia, the patient underwent a right fronto-orbital craniotomy as described by Jane *et al*[26] with removal of the right orbital apex mass. Pathology was again consistent with the diagnosis of paraganglioma. The procedure was terminated when tumour-free margins were obtained.

Discussion

Paraganglioma of the orbit is a rare tumour with 27 such cases reported in the literature.[1-23]

The pathological differential diagnosis of orbital paraganglioma includes meningioma, metastatic adenocarcinoma (especially renal cell carcinoma) alveolar soft part sarcoma, aveolar rhabdomyosarcoma, and hemangiopericytoma. Ultrastructural demonstration of neurosecretory granules in the chief cells of paraganglioma is diagnostic.

The MR images allowed further characterisation of the tumour mass, in that the salt-and-pepper appearance of the matrix is strongly suggestive of the diagnosis of paraganglioma.[25] Prominent vessels might occur in association with other intraconal orbital masses, especially cavernous haemangioma, although this has not yet been described in reported cases.[27-29] Intraorbital meningiomas usually do not have grossly enlarged vessels that can be demonstrated by CT or MRI. Optic nerve glioma would not have a salt and pepper matrix or prominent vascularity. Intraorbital metastases are usually not sufficiently hypervascular to have grossly enlarged vessels associated with them.[30]

While surgery is the treatment of choice for paragangliomas radiation therapy for unresectable or incompletely resectable tumours, unencapsulated tumours, and for recurrence has been generally recommended.[31] Tumour regression has been demonstrated using this procedure[10] though at least one case report failed to note any effect of postoperative radiotherapy (5000 cGy) on tumour size.[2] However there was no discussion regarding the effect of radiation therapy on the patient's symptomatology.

In summary this report reviews the pertinent literature to date and presents the pathological and radiological appearance of an orbital paraganglioma including the first MR description to our knowledge. Although rare in this location a paraganglioma should be considered in the differential diagnosis of a vascular orbital mass.

We acknowledge the referral of this patient by Dr Richard L Dallow and the illustrations provided by Rolf Sennhenn, COT, CRA.

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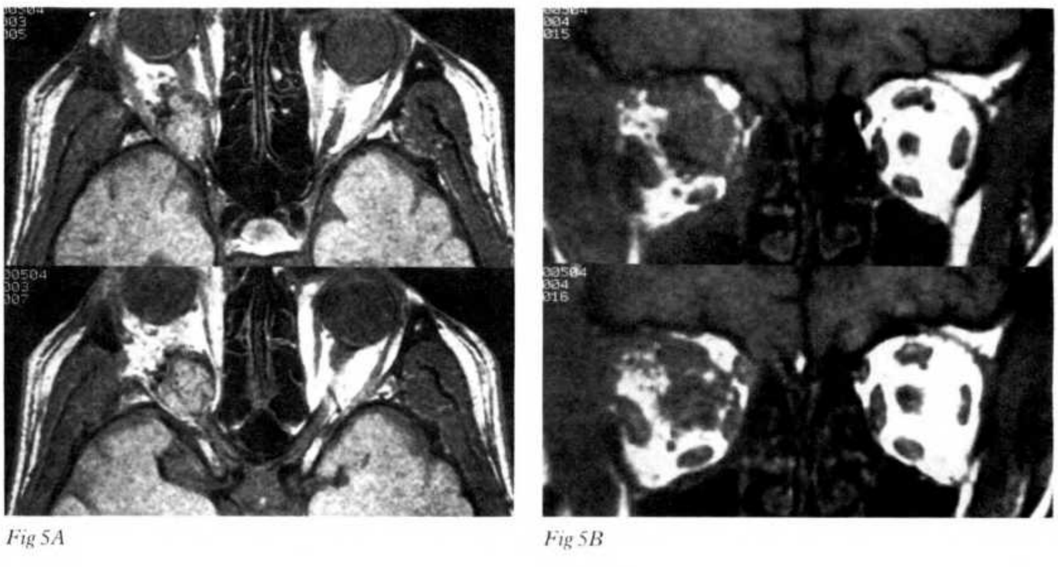

Figure 5 A, B Axial and coronal MR scans of the orbits demonstrate a well defined tumour mass in the muscle cone, sitting above and lateral to the right optic nerve (A; TR 2500 ms, TE 30 ms). Punctate and serpiginous structures with flow voids represent prominent arteries and veins associated with the tumour (A). Note also the lateral orbitectomy defect in A and B. Coronal T1-weighted spin echo image (B; TR 600 ms, TE 20 ms) confirms intraconal location of the mass.

Fig 5A *Fig 5B*

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Nettleship collaterals: circumpapillary cilioretinal anastomoses after occlusion of the central retinal artery

Nicola K Ragge, William F Hoyt

Abstract

In extremely rare cases, after occlusion of the central retinal artery, a complete ring of peripapillary anastomotic channels develops. One such case is described and a proposed term given to these channels – 'Nettleship collaterals' – after the man who first described them. These collaterals are dilated pathways within the terminal capillary networks of the posterior ciliary arteries and the branches of the central retinal artery. Formation of the channels is believed to be promoted by prelaminar obstruction of the central retinal artery.

A century ago at St Thomas' Hospital, London, Nettleship[1] illustrated the ophthalmoscopic appearance of circumpapillary arterial collaterals in a patient with an occluded central retinal artery. He described these collaterals as occurring between the 'sclerochoroidal ring' and branches of the central retinal artery.

Fourteen years later in Lausanne, Gonin[2] published a similar drawing. The branches of the central retinal artery were narrowed proximally on the optic disc and then after a short retinal course widened abruptly to almost normal calibre. A succession of 'petites anses ou de crochets' (small hooks) could be seen emerging from the margin of the disc and joining the main arterial branches at their points of enlargement. Indeed some of the arterial branches were fed by a confluence of several collaterals.

Although limited peripapillary arterial collaterals occasionally form after occlusion of the central retinal artery or one of the main branches on the disc,[3-9] documentation of complete rings of these collaterals is rare. Since Nettleship and Gonin these exceptional cases have appeared in the form of sketches,[10] colour photographs,[11 12] a description with no illustration,[13] and fluorescein angiograms.[12 14]

A new case of circumpapillary cilioretinal arterial collaterals surrounding an anteriorly obstructed central retinal artery is discussed and recorded photographically. The term 'Nettleship collaterals' is proposed for these anastomotic channels.

Case history

An 85-year-old woman was examined 8 months after an occlusion of her right central retinal artery, which left her with no light perception in her right eye. Her general health was otherwise good and she did not have hypertension, diabetes, or valvular heart disease. She was taking aspirin, 150 mg daily and prednisolone, 5 mg daily. Her visual acuity was 20/30 (corrected) in the left eye.

Her right optic disc (Figs 1 and 2) was pale and atrophic. It was surrounded by a distinctive corona of multiple arterial-to-arterial collaterals. These collateral vessels arose from just within the disc margin and via a tortuous route joined and supplied the branches of the retinal artery in the peripapillary zone. In some instances the collaterals appeared to take a spiral course (for example, the vessel at 1 o'clock) or were coiled initially and then straightened just before joining the retinal arterial branch (for example, the vessel at 11 o'clock). One collateral (at 10 o'clock) arose from inside the disc margin in a

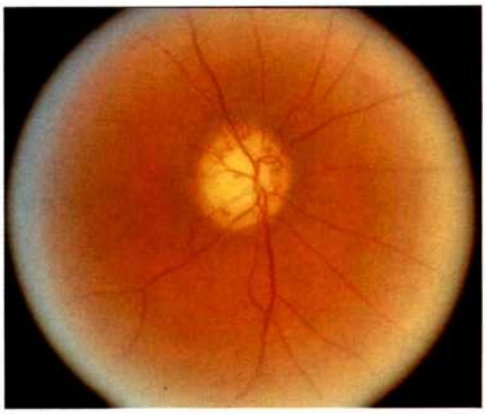

Figure 1 Photograph of the right fundus of the patient 8 months after occlusion of the central retinal artery, showing 'Nettleship collaterals'.

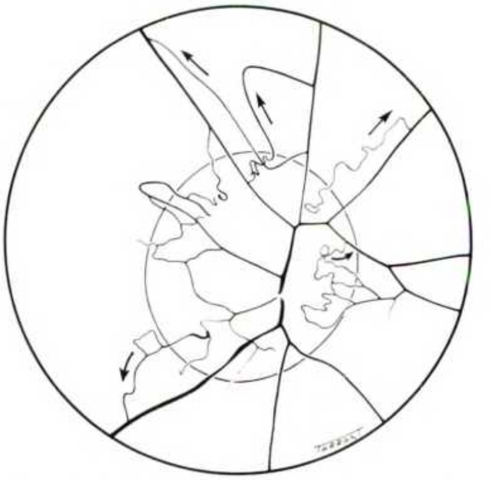

Figure 2 Diagram of the right fundus of the patient to illustrate with further clarity the 'Nettleship collaterals'. Arrows indicate the presumed direction of blood flow within them.

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similar way to the others, traversed the disc margin, and then looped sharply back on itself to anastomose with a small direct branch from the central retinal artery. In general the retinal arterial branches were attenuated and had significant irregularity of calibre; this irregularity was especially prominent in the inferior branches. Where the branches were joined by the collaterals some attained a wider calibre (for example, those at 12 o'clock and 1 o'clock). The central retinal artery appeared on the disc as a ghost vessel, and the initial segments of its main branches contained only a narrow column of blood: most of their lumens appeared to be occluded. Fluorescein angiography showed that filling of both retinal and choroidal circulation was markedly delayed: dye first appeared 28 seconds after the injection. Both circulations were filled simultaneously.

In the left fundus there was evidence of occlusion of a superior branch of the retinal artery as well as age-related macular degeneration. The results of investigations for temporal arteritis and heart disease were negative but carotid doppler studies revealed 50% stenosis of the right carotid artery and haemodynamically insignificant disease of the left carotid artery.

Discussion

'Nettleship collaterals' are multisectorial cilioretinal collateral vessels that arise from posterior ciliary vessels in the optic disc, course over the edge of the disc, and join the branches of the retinal artery in the peripapillary area. These collaterals form, after occlusion of the central retinal artery, by enlargement of selected channels within the capillary networks already existing in the optic disc and in the peripapillary superficial nerve fibre layer. The networks are supplied by the posterior ciliary arteries and the proximal trunks of the retinal artery.[14 15] Although there appears to be significant flow in these vessels Nettleship collaterals usually represent an ineffective attempt to revascularise the retina via the posterior ciliary circulation after occlusion of the main stem of the central retinal artery. Presumably the attempt at revascularisation fails for two reasons. First, the amount of blood flow is insufficient; second, it reaches the retina after the death of the retinal neurons. In most reported cases (Table 1) the eyes remain totally blind unless a cilioretinal artery is present. One patient with well-maintained visual acuity, described by Marmor and colleagues,[12] is an exception to the preceding generalisations.

Table 1 Summary of clinical details for reported patients with Nettleship collaterals after occlusion of the central retinal artery

Author (year)	*Age of patient (sex)*	*Valvular heart disease*	*Carotid artery disease*	*Hypertension*	*Visual acuity after CRAO*	*Time from occlusion to first detection of collateral formation*
Nettleship (1891)[1]	? (M)	?	?	?	?	12 months
Gonin (1905)[2]	64 (F)	+	–	–	NLP	3 months
Harms (1914)[13] (case 3)	47 (F)	+	–	–	HM†	11 months
Jensen (1938)[10] (case 2)	61 (M)	+	–	+	CF, then 6/12*	24 months
Larsen (1969)[11]	40 (M)	–	–	+	NLP	3 months
Hayreh (1969)[14]	14 (F)	–	–	–	?	9 months
Marmor *et al* (1985)[12]						
Case 1	69 (M)	–	+	–	6/6	?
Case 2	67 (F)	–	–	+	6/60	?
This case (1991)	85 (F)	–	+	–	NLP	8 months

*Cilioretinal artery present †No illustration supplied. CRAO=central retinal artery occlusion, NLP=no light perception, HM=hand movements, CF=count fingers

Data from experiments on cats[16] and rhesus monkeys[17] and from observation of patients[7 9] suggest that collaterals probably develop within days or weeks after occlusion of the central retinal artery, although in most reported cases they are only detected months later. Presumably the vessels become more conspicuous in the later stages because of their increasing width and their increasing contrast to an optic disc that is becoming atrophic.

Formation of collaterals around an obstructed central retinal artery is promoted by several factors: complete obstruction of the vessel;[17] a suitable pressure gradient in the alternative blood supply, here the branches of the posterior ciliary artery;[16] and possibly local vasoproliferative factors stimulated by ischaemia in the peripapillary retina.[7] Complete obstruction of the central retinal artery can be caused by different types of emboli or by thrombosis. Calcific emboli (making up 9% of all emboli) have been traditionally associated with more severe and permanent visual loss and with the formation of collaterals.[7] In fact valvular heart disease, the most frequent source of calcific emboli, was present in many of the reported patients with Nettleship collaterals.[2 10 11] Cholesterol emboli can also be the cause of sectorial peripapillary collaterals.[7] In this patient atheromatous disease of the carotid artery may have been the source of the embolus. The cilioretinal collaterals described by Hayreh[14] were seen in a 14-year-old girl whose central retinal artery was occluded as a result of herpes zoster ophthalmicus. Presumably the mechanism of occlusion in that patient was arteritis combined with *in situ* thrombosis.

What then are the special circumstances that promote the formation of Nettleship collaterals? There are two possible causes: a rare anterior site of occlusion or a rare anatomical variation.

In the first situation, as suggested by Nettleship[1] in his original description, the central retinal artery is obstructed at an unusually anterior site. Obstruction of the central retinal artery most commonly occurs behind the lamina cribrosa.[18 19] The central retinal artery then refills, either by recanalisation or via presumed anastomotic vessels[14 15 17 20–25] from the posterior ciliary circulation, sometimes indirectly via pial branches. These anastomoses form anterior to the obstruction but too deep to be visible on the surface of the disc. However if the obstruction is anterior to the lamina cribrosa the anastomoses are unable to feed into this section of the central retinal artery. This forces the formation of alternative cilioretinal collaterals from the rim of the disc. The anterior occlusion is visible on the disc in this case and in other cases of Nettleship collaterals.[1 14] Further, an anterior embolus was visible in all of the cases of sectorial collateral formation after retinal artery occlusion described by Arruga and Sanders[7] and in some additional reported cases.[4 10]

The second possible reason for the formation of Nettleship collaterals depends on the wide variations in branches of the central retinal artery and posterior ciliary arteries.[26] It may be that in rare individuals no potential exists for communication between these two vascular networks except in the peripapillary area. In such cases communication would open up in this area after obstruction of the central retinal artery regardless of the site of occlusion.

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Complicated migraine resulting in blindness due to bilateral retinal infarction

Andrew M Glenn, Pamela J Shaw, John W Howe, David Bates

Abstract

Retinal migraine is not uncommon, but permanent sequelae in the anterior visual pathway are rare. We describe the case of a young woman in whom blindness developed over a six-year period due to recurrent episodes of migraine-related occlusions of a branch retinal artery.

Migraine occurs in 10–25% of the population[1] and is more common in women than in men. 'Complicated migraine' occurs in 1% of cases and is defined as an episode of classical migraine which results in a persisting neurological deficit.[2] Persisting visual morbidity in migraineurs is usually caused by posterior cerebral hemisphere ischaemia.[3] Permanent anterior visual pathway damage related to migraine has been reported rarely. Several types of migraine-related retinal vascular lesions have been described, including branch retinal artery occlusion (BRAO),[4-8] central retinal artery occlusion,[4 7 9-11] ciliary artery occlusion,[12] anterior ischaemic optic neuropathy,[13-15] and central retinal vein thrombosis.[12 16] Other retinal abnormalities described as migraine related include; optic nerve haemorrhage,[17] disc oedema and retinal haemorrhage,[18] inner retinal layer damage,[19] optic atrophy,[4] and neuroretinitis.[4]

We report a case of a young woman who had recurrent attacks of migraine-related BRAO affecting both eyes and resulting in legal blindness

Case report

A 20-year-old housewife began experiencing classical migraine at the age of 14 years. She was initially treated with propranolol as a prophylactic agent. At the age of 15 in association with a typical migraine attack she developed profound and persisting loss of vision in the left eye. The visual actuity of the affected eye was reduced to perception of light, and only the superotemporal quadrant of vision remained intact. Funduscopy revealed an acute occlusion of the superotemporal, superonasal, and inferotemporal arteries. The left sided visual loss persisted despite treatment with acetazolamide, amyl nitrate, and CO_2 rebreathing.

Eight months later, following an increase in the frequency of her migraine, she developed an occlusion of a macular branch of the right superotemporal arteriole which resulted in a permanent scotoma and a reduction of visual acuity on the right to 6/9.

At the age of 20, again following an increase in the frequency of her migraine, she suddenly developed further loss of vision in the right eye due to an inferotemporal BRAO affecting the macula (Fig 1). On this occasion she was treated with the calcium channel blocker nimodipine and intravenous methyl prednisolone 1 g daily for three days. No visual recovery occurred.

The patient had not been taking an oral contraceptive agent and had never been prescribed ergot derivatives. Her father, brother, and niece also suffer from migraine.

EXAMINATION

A general medical examination revealed no significant abnormalities. In particular she was normotensive, the heart was clinically normal, and there were no carotid or orbital bruits. Slit-lamp examination revealed normal anterior segments, and the intraocular pressures were 14 mm Hg in both eyes. After the most recent BRAO her visual acuity was counting fingers in the right eye and hand movements in the left. There was loss of the central and superotemporal visual field of the right eye and loss of all but the superotemporal quadrant of the left. Funduscopy showed an acute occlusion of the inferotemporal arteriole on the right and optic atrophy plus attenuation of the superior and inferior temporal arterioles on the left. A fluorescein angiogram, performed on the right eye two days after the inferior temporal BRAO (Fig 2) showed occlusion of the inferotemporal arteriole and evidence of the previous superior macular branch arteriolar occlusion.

INVESTIGATIONS

The following investigations gave normal or negative results: full blood count, erythrocyte sedimentation rate, routine biochemical screen-

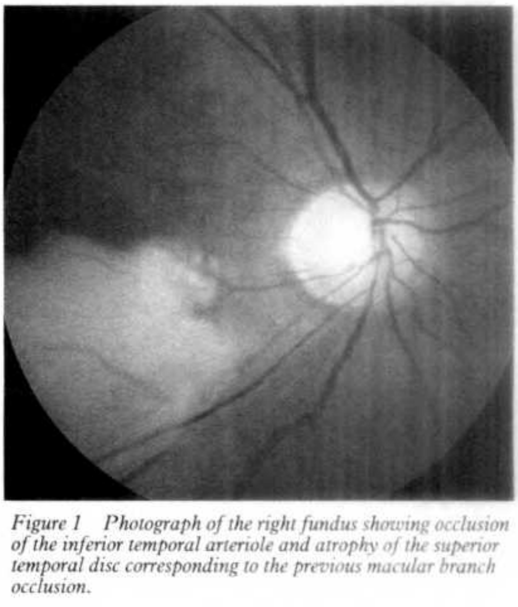

Figure 1 Photograph of the right fundus showing occlusion of the inferior temporal arteriole and atrophy of the superior temporal disc corresponding to the previous macular branch occlusion.

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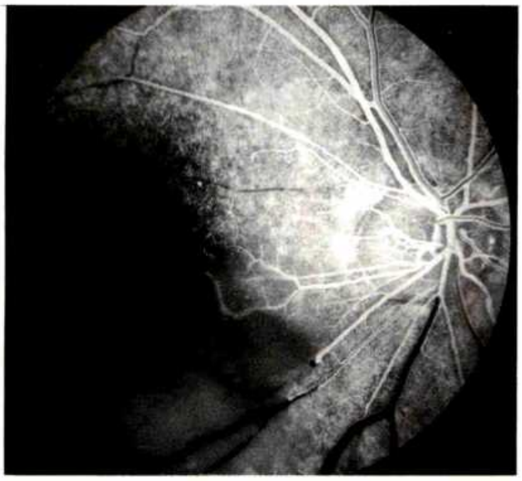

Figure 2 Fluorescein angiogram of the right eye showing occlusions of the inferotemporal and superior macular branch arterioles.

ing tests, VDLR/TPHA, autoantibodies including anticardiolipin antibodies and DNA binding, fasting blood lactate and pyruvate and lactate/pyruvate ratio, serum angiotensin converting enzyme, full clotting studies including prothrombin time, activated partial thromboplastin time, platelet function studies, protein C, protein S, levels of factors V and VIII and lupus anticoagulant, fasting cholesterol, and triglycerides. A chest radiograph and electrocardiograph were normal, and M-mode and two dimensional echocardiography gave normal findings, with no evidence of a cardiac embolic source. A cranial CT scan was normal and the cerebrospinal fluid showed normal levels of protein, IgG, glucose, and cells. A Colour Flow Duplex Scan (an ultrasound and doppler haemodynamic study) revealed normal flow and morphology in the carotid arteries.

Discussion

In the elderly BRAO is usually due to emboli from atheroma at the carotid bifurcation.[20 21] In younger patients systemic disorders associated with retinal vasculitis, such as sarcoidosis and collagen vascular disease, may lead to BRAO.[22]

In a series of 27 cases of retinal artery occlusion occurring under the age of 30 years risk factors were identified in the majority and included coagulation or platelet disorders, heart disease, or the use of oral contraceptive agents.[5] Migraine was the sole risk factor for retinal stroke in only two (7%). Gass *et al*[23] recently reported on a series of nine patients (age range 24–69 years) with idiopathic recurrent BRAO. The fundal appearances were suggestive of focal arteritis and arteriolitis. Most of these patients retained good central vision, and none developed evidence of systemic vascular disease.

BRAO secondary to retinal migraine can be diagnosed when the retinal infarction occurs during an attack of migraine and other risk factors for retinal vascular occlusion have been excluded. The pathogenesis of retinal vascular occlusion in migraine is incompletely understood. The most widely accepted theory is that there is an episodic reduction in retinal blood flow, due to vasospasm and/or vessel wall oedema.[24] This may be associated with a thrombotic predilection because of abnormalities of platelets, plasma, and/or blood vessels.[25]

In our case after episodes of BRAO vasodilators, calcium channel blockers, intravenous steroids, and measures to reduce intraocular pressure were ineffective in ameliorating the visual loss. Furthermore antimigraine prophylaxis with ß blockers and serotonin antagonists did not prevent further attacks. The usefulness of antiplatelet agents, particularly for prevention of migraine related infarcts, requires evaluation. There is recent animal experimental evidence that glutamate antagonists given after cerebrovascular occlusion may reduce the area of cerebrovascular damage.[26] Such agents may be of value in limiting the area of infarcts following retinal vascular occlusions.

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LETTERS TO THE EDITOR

Use of a modified back-flush needle in diabetic vitrectomies

SIR, — A safe method for removal of blood from the vitreous cavity is a prerequisite to performing successful surgery particularly in eyes with advanced proliferative diabetic retinopathy. Such eyes often have dense retrohyaloid haemorrhage and tractional retinal detachments. The vitreous haemorrhage often settles in a viscous layer on atrophic detached retina and thus makes 'vacuuming' with a conventional Charles flute needle potentially hazardous.

Zivojnovic described the use of the modified back-flush needle[1] which incorporates a silicone rubber bulb with an aperture for control of suction, and which also permits reflux of intraocular fluid. Although this modification was designed to free any incarcerated tissue such as retina we describe a technique which facilitates complete removal of blood from the vitreous cavity and preretinal space with safety.

Any integral haemorrhage present is first removed by conventional three-port vitrectomy. An opening can then be produced into the posterior hyaloid space through which the back-flush needle can be positioned under direct visualisation; fluid haemorrhage is then evacuated using the flute modality of the needle (Fig 1a). In addition to aid complete clearance of settled blood, particularly prior to epiretinal membrane dissection or to endophotocoagulation, the rubber bulb can be forcefully depressed with the forefinger over the aperture, creating a jet of fluid directed at the layered blood on the retinal surface (Fig 1b). The current of the fluid blows the settled blood off the surface of the detached retina. The blood immediately disperses and circulates mostly in the anterior part of the vitreous cavity, and can then be easily vacuumed from there using the same flute needle.

Peyman described a similar technique in which the exit aperture of the flute needle is tapped with the index finger causing the pressure within the cannula to be increased expelling the needle's contents inside the eye.[2] Though no complications were described with this procedure the number of cases was small and we believe that the technique we describe is more controlled and hence safer.

We have now used the back-flush needle technique for more than 2 years on more than 150 cases with traction retinal detachments due to proliferative diabetic retinopathy. So far we have not encountered any complications, in particular no iatrogenic retinal breaks have been created as a result of this procedure.

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We thank Mr T Tarrant for kindly providing the figure.

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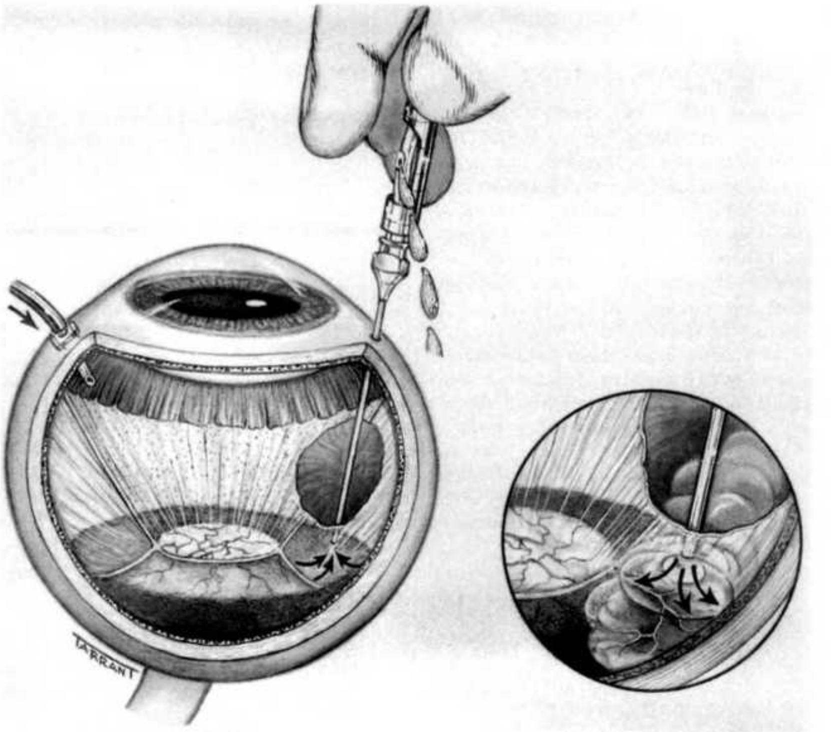

Fig 1a

Fig 1b

An opening through the posterior hyaloid has been made. Evacuation of retrohyaloid haemorrhage using the flute needle modality (a), and dispersion of settled haemorrhage from the retinal surface using the back-flush modality (b).

Scleral melting and conjunctival rhinosporidiosis

SIR, — I read with interest the case report by De Doncker *et al.*[1] A retrospective study (unpublished) of 28 cases of ocular rhinosporidiosis seen at the Government Ophthalmic Hospital, Madras, between 1978 and 1986 included a 32-year-old male who presented with a slowly progressive bluish swelling on the temporal sclera of the left eye. There was no past history of significant ocular disease or injury.

Clinical examination revealed scleral ectasia of about 5 mm in diameter temporal to the limbus. Overlying this area there was a vascularised conjunctival polyp of approximately 3 mm in diameter at the base and clinically diagnosed as rhinosporidiosis because of characteristic pale spots scattered on the surface. This patient was treated by excising the conjunctival lesion (histopathological examination confirmed the clinical diagnosis) and scleral grafting over the area of scleral weakness. The status of the disease process in the late postoperative period was not recorded as the patient was lost to follow-up – a common occurrence in Indian government hospitals.

To my knowledge there are 20 cases of scleral staphylomas associated with histologically proved conjunctival rhinosporidiosis[2-4] other than the one described above and the two cited by De Doncker *et al.* One of the management options reported initially was excision of the conjunctival granuloma over the scleral staphyloma and the use of a conjunctival flap to strengthen the area of scleral thinning.[3] This prevented an increase in the size of the staphyloma when the patient was reviewed at 6 months. More effective treatment was suggested by Kuriakose in 1972 (paper presented at the 29th All India Ophthalmic Society Conference) in the form of pushing the staphyloma inwards and suturing the healthy scleral edges together or using a corneal graft to cover the scleral defect. However by 1980, based on the experience of treating four[5] and seven[6] cases, a consensus had emerged as to the most successful management of scleral staphylomas caused by conjunctival rhinosporidiosis: excision of the overlying conjunctival granuloma, reduction in the size of the staphyloma by administering oral acetazolamide, performing anterior chamber paracentesis, and gentle pressure on the surface of the staphyloma followed by the use of a reinforcing donor scleral graft which extends beyond the margins of the scleral staphyloma. Finally the healthy conjunctival edges are sutured over the scleral graft. There was no case of recurrence on long-term review of the operated patients.[1-6]

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Topical timolol and serum lipoproteins

SIR, — Although West and Longstaff failed to find any significant alterations in serum lipids with topical ophthalmic timolol use in a group of 17 patients treated for 15 weeks their study does not have an adequate power to give confidence that this is a true result.

Studies should be designed to have an 80% power to detect a change if one is induced via experimental perturbation. In general for studies of drug induced effects on serum lipids this requires a patient population of about 30.

We performed a study[1] with 28 volunteers which had a design power of 80% to detect a change of 0·15 mmol/l in high density lipoprotein (HDL) cholesterol. We determined that topical ophthalmic timolol treatment caused a 9% decrease (0·14 mmol/l) in HDL cholesterol ($p<0{\cdot}001$).

West and Longstaff's study had less than 50% power to detect a difference in HDL cholesterol levels of the magnitude that we have demonstrated when the study power is calculated with their reported standard deviations. This is far too low to assume no effect of an experimental treatment.

In addition a more appropriate analysis of their data would have been a paired *t* test, since each patient served as his own control in the study. With the paired *t* test their results might have been closer to statistical significance. Study power would have however remained unchanged (low).

Further, studies of drug induced lipid effects should state explicitly the degree of standardisation of their lipid analysis laboratory throughout the study. Lipid assays are notoriously variable. Failure to maintain a sufficient level of standardisation throughout a study of drug induced lipid effects may greatly reduce the ability of a study to detect the sought after effect even in studies designed for adequate power.

The consequences of lowering HDL cholesterol levels must be seriously evaluated because the HDL cholesterol level is a definite risk factor for cardiovascular disease. A small reduction in HDL cholesterol which occurs in a large number of individuals shifts the distribution of HDL cholesterol levels for the whole population. Such a lowered distribution would be associated with an increased risk of coronary heart disease in that population as a whole no matter how small the individual reduction in HDL cholesterol. As physicians we must be concerned about the population attributable risk associated with the therapy that we prescribe. Millions of people are presently using topical β blockers.

Certainly additional larger studies of ophthalmic β-blocker induced effects on serum lipids are needed. Is the effect on HDL cholesterol different in a population of glaucoma patients? Is the effect seen with all β blockers? Is it affected by nasolacrimal occlusion? Does the effect increase or decrease with exposures of longer than 2 months? Is the effect reversible on stopping therapy?

Finally, it would be of interest for your readers if sources of study funding were indicated.

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1 Coleman AL, Diehl DLC, Jampel HD, Quigley HA, Bachorik PS. Topical timolol decreases plasma high density lipoprotein cholesterol level. *Arch Ophthalmol* 1990; **108:** 1260–3.

Reply

Sɪʀ,—The study population required to give adequate power depends on the magnitude of the minimal change one wants to detect and therefore one cannot make generalisations about the size of the study population required until the level of minimal change to be detected is agreed. (The change in serum concentration of high density lipoproteins (HDLs) which it is worthwhile detecting with regard to the risk of coronary heart disease remains to be determined.[1])

As stated in our paper[2] we looked primarily at serum triglyceride (TG) levels as one would expect the number of patients to give adequate study power to detect any effect on serum TG levels of topical timolol treatment to be smaller than if looking for an effect on serum HDLs as HDL levels are affected only half as much as TG levels in systemic studies. It is of interest that although Coleman *et al*[3] demonstrated highly significant change in serum HDLs they failed to show high significance for the change in serum TGs measured.

Our study in a group of patients with glaucoma had more than 90% study power at 5 weeks to detect a change of 0·3 mmol/l in serum TGs; at 15 weeks study power was just under 80% to detect a similar change.

Surprisingly study power for an HDL change of 0·14 mmol/l at 5 weeks was >95% and at 15 weeks for the same change was >80%. The study power was adequate for a smaller change in HDLs compared with TGs due to the much smaller standard deviation for HDL changes.

Our statistician agrees that a paired *t* test is more appropriate but recalculation using this test as expected does not make any of the changes significant.

Our lipid analysis was carried out using Technicon methodology on a COBAS BIO centrifugal analyser as stated in our paper. Standardisation for this system is according to the the Centres for Disease Control criteria.

The study was funded within the departments of ophthalmology, biochemistry and community medicine of the hospital and we are grateful for the help of our colleagues in completing the work.

As with other lipid related cardiovascular studies we agree with the need for a larger study population so as to be able to evaluate fully any possible effect of a treatment (topical β blockers in this case) on serum lipids and consequent influence on risk of coronary heart disease. To this end a multicentre study would offer the most certain means of determining any possible influence.

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BOOK REVIEW

Les Strabismes: De l'analyse clinique a la synthese chirurgicale. 2nd edn. By Annette Spielmann. Pp 292. 419F. Masson: Paris, 1990.

This is the second edition of a French textbook on strabismus written by Madame Annette Spielmann, a leading French strabismologist. The first edition was published in 1989 and the new edition has been reviewed and re-edited.

This is an excellent and comprehensive account of strabismus by one author, well illustrated with diagrams and photographs and with a comprehensive bibliography. In common with most works within the European tradition, more attention is paid to the sensory aspects of strabismus and there is interesting material on dissociated deviations and supranuclear palsies. Madame Spielmann deals briefly but firmly with the eccentric therapy widely popular in France of sector treatment of amblyopia and strabismus, with which she does not agree.

British readers will find the layout of the chapters unusual in that subjects are treated much more from an aetiological than an anatomical point of view and this is in itself refreshing and stimulating. Although I would not recommend this book as a first text on strabismus, those with an interest will find it well worthwhile.

J P LEE

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NOTES

Professor Hans Goldmann, MD

We regret to report that Professor Hans Goldmann died on 20 November 1991. We hope to have an obituary in a later issue.

8th International Steglitz Paediatric Surgical Congress 1992 Berlin/Germany

The 8th International Steglitz Paediatric Surgical Congress will be held on 4–5 December 1992 at the University Medical Centre, Steglitz, Berlin. Under the title 'Endoscopical surgery in children' it will be chaired by Professor Dr J Waldschmidt. Further information: PD Dr F Schier, Kinderchirurgie, Univ-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. (Tel: 030 798 4181 or 798 2909. Fax: 030 798 4141.)

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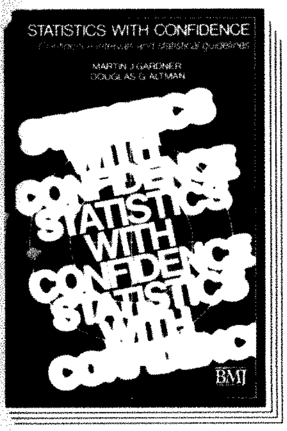
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